

Diabetes, Osteoporosis, and Fractures

BY ROBERT G. JOSSE, MD, FRCPC

For some time it has been recognized that people with diabetes are at increased risk for fracture, especially peripheral fractures. Type 1 diabetes mellitus (T1DM) tends to be associated with reduced bone density (BMD), whereas in type 2 diabetes (T2DM) the BMD is normal or increased, yet fractures still occur. Understanding the pathophysiology of this association is still evolving, but it is clear that certain drugs commonly used for the treatment of T2DM ie, the thiazolidinediones (TZDs), increase the fracture risk, particularly in women. This issue of *Endocrinology Rounds* outlines the current understanding in relevant aspects of bone biology, explores the mechanisms whereby TZD drugs may interfere with bone metabolism, and presents the limited clinical data available. Indeed, this is an area of great current interest: the encounter of two chronic conditions – diabetes and osteoporosis/fractures.

Bone biology update

Bone is a dynamic tissue; its resorption and formation is a continuous process throughout life.¹ Since all materials subjected to repeated cyclical loading can suffer stress fatigue (eg, microscopic cracks), the skeleton is no exception, but unlike bridges and airplanes, the skeleton can repair itself. The process of self-repair is called remodeling and is clearly essential for the preservation of the mechanical strength of bone. Throughout the skeleton, bone turnover occurs in discreet microscopic packets of bone, termed basic multicellular units (BMUs) in both trabecular and cortical bone. The major cells of the BMU are the osteoblasts (bone-forming cells, derived from mesenchymal stem cell precursors), and osteoclasts (bone-resorbing cells, derived from hematopoietic, monocyte/macrophage stem cell precursors).² The cycle of resorption and formation is an orderly coupled process that is primarily mediated by signals from the osteoblast (Figure 1).³ A variety of circulating and local factors (eg, hormones, growth factors, cytokines) act on the osteoblasts and cause the production of the receptor activator of nuclear factor κB ligand (RANKL), a cytokine that interacts with RANK receptors on nascent osteoclasts (Figure 2). The osteoblasts then signal the differentiation of osteoclast precursors and recruitment of osteoclasts, causing resorption of a small packet of bone.³ After a short period of time (2-3 weeks) osteoclasts undergo apoptosis and osteoblasts then move in to occupy the resorption cavity, depositing a cement line and synthesizing new matrix (osteoid), which then becomes mineralized. The osteoblasts also start secreting osteoprotegerin (OPG), a decoy receptor, to block the osteoclast activity of bone resorption (Figure 3).³

It takes several months to deposit and mineralize the area of resorbed bone. As new bone is synthesized, some osteoblasts are buried in the newly formed bone and become osteocytes; increasing evidence suggests that osteocytes are the primary sensor of mechanical stress and load on the skeleton. Osteocytes are connected with each other and to the bone surface through a network (syncytium) of fluid-filled channels, which, among other things, transduce mechanical signals necessary for adaptive modeling and remodeling in the face of changing loads.

In summary, osteoblasts produce the signals for recruiting osteoclasts and regulating osteoclast activity, synthesize the collagen matrix of bone, and produce enzymes and



Leading with Innovation
Serving with Compassion

St. Michael's Hospital

A teaching hospital affiliated with the University of Toronto



Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

LAWRENCE LEITER, MD (HEAD)
EDITOR, ENDOCRINOLOGY ROUNDS

ANDREW ADVANI, MD, PHD

GILLIAN BOOTH, MD

ALICE CHENG, MD

PHILIP CONNELLY, PHD

CHRISTINE DERZKO, MD

RICHARD GILBERT, PHD, MD

JEANNETTE GOGUEN, MD

LOREN GROSSMAN, MD

AMIR HANNA, MD

DAVID JENKINS, MD, PHD

ROBERT JOSSE, MD

MARIA KRAW, MD

TIM MURRAY, MD

DOMINIC NG, PHD, MD

JOEL RAY, MD

WILLIAM SINGER, MD

VLAD VUKSAN, PHD

QINGHUA WANG, MD, PHD

TOM WOLEVER, MD, PHD

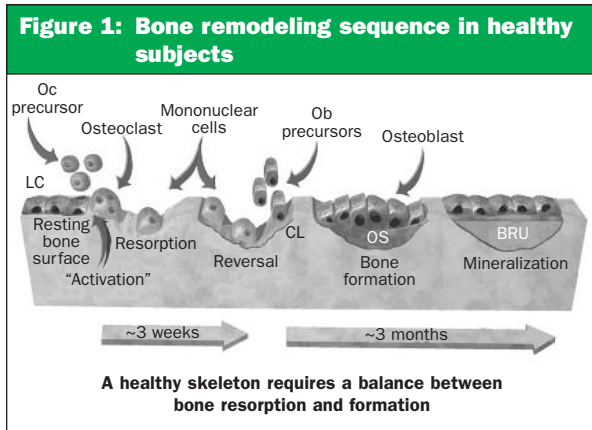
MINNA WOO, MD, PHD

CATHERINE YU, MD

St. Michael's Hospital

6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

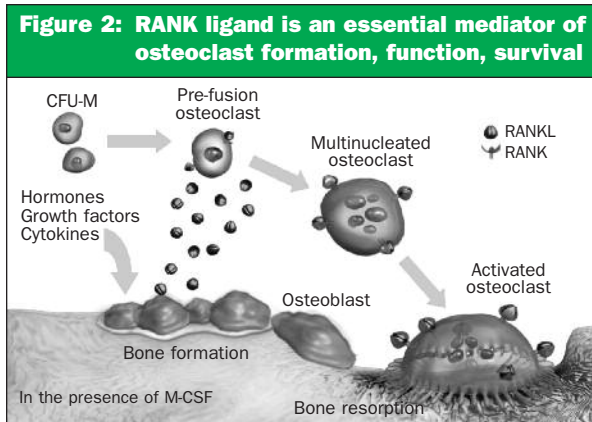
The opinions expressed in this publication do not necessarily represent those of the Division of Endocrinology and Metabolism, St. Michael's Hospital, the University of Toronto, the educational sponsor, or the publisher, but rather are those of the author based on the available scientific literature. The author has been required to disclose any potential conflicts of interest relative to the content of this publication. *Endocrinology Rounds* is made possible by an unrestricted educational grant.



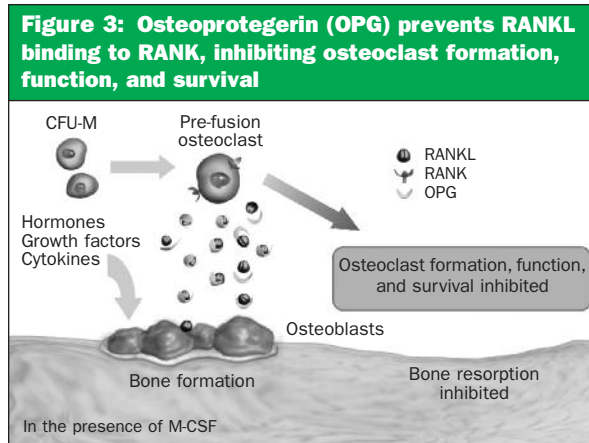
LC = lining cells; CL = cement line; OS = osteoid; BRU = bone remodeling unit

other proteins necessary for regulating the mineralization process. During this remodeling cycle, the active cells synthesize proteins that can be measured as markers of the osteoblast formation process; for example, some osteoblast products can be used as a measure of bone formation (eg, osteocalcin, bone-specific alkaline phosphatase, propeptides of type I collagen). Further, osteoclast activity releases proteins, which are the products of osteoclast-mediated bone resorption; usually, these are residues of collagen breakdown, eg, serum C- and N-telopeptides, and both can be measured as markers of bone resorption (Table 1).

Modeling and remodeling the skeleton is necessary during growth to achieve peak bone mass and strength. In adulthood, remodeling is required to maintain that strength by identifying areas of old and microdamaged bone, removing it, and replacing it with new bone. Through this process of asynchronous remodeling, nearly 5% to 10% of the skeleton is “turned over” per year. Bone is a remarkable structure because it is stiff yet flexible, strong but light, and its anatomical struc-



RANK = receptor activator of nuclear factor κ B; RANKL = RANK ligand; CFU-M = colony forming unit macrophage; M-CSF = macrophage colony stimulating factor



ture determines the loads bone can bear and, in turn, the loads help to determine the anatomical structure. Recently, much has been learned about the physiology of bone and, more particularly, the cells involved and their intricate interactions. The bone-remodeling sequence and, hence, bone turnover are relatively slow in adulthood before menopause, but accelerates during the perimenopause and postmenopausal years for a variable period of time (~5 years) during which bone remodeling balance becomes more negative.⁴ Abnormalities or an imbalance in this remodeling activity form the basis for the development of metabolic bone diseases such as osteoporosis.⁵ Understanding the pathophysiologic process itself and appreciating the properties of the cells involved has allowed the development of treatments to protect the skeleton and help prevent fragility fractures.⁶ While the same principles of bone biology apply to diabetes, certain aspects are poorly understood, particularly the relationship between the type of diabetes and metabolic control of various changes in bone mass, structure, and strength.

Table 1: Biochemical markers of bone turnover

BONE FORMATION
*Serum bone specific alkaline phosphatase (BSAP)
Serum osteocalcin
Serum carboxy-terminal (C) and amino-terminal (N) propeptides of type I collagen (P1CP and P1NP)
BONE RESORPTION
*Serum and/or urine C- and N-telopeptides of collagen (CTX & NTX)
Urinary excretion of pyridinium cross-links of collagen (e.g. deoxypyridinoline)

* Most commonly measured

Epidemiology of diabetes, osteoporosis and fractures

Around the age of 50, a white woman in the United States has a remaining lifetime risk of 16% for suffering a hip fracture, and a 32% chance of a vertebral fracture.⁷ Bone health is further compromised in people with both T1DM and T2DM. Bone density is often reduced in patients with T1DM, but it is usually normal or even increased in T2DM.^{8,9} The relationship between diabetes and fracture risk is not clear-cut, but it appears to increase in most studies of patients with T1DM.¹⁰ Some epidemiological studies have described a 6.9- to 12-fold increase in the relative risk of hip fracture among women with T1DM compared with those without, but the situation with T2DM is inconclusive.^{11,12} Given the increased body mass index (BMI; ie, obesity) in most patients with T2DM, a decrease in hip fractures may be expected because:

- increased fat mass would act as “padding” absorbing the energy of a fall
- greater weight would maintain hip strength through increased skeletal loading
- bone mass would be enhanced by increased endogenous estrogen production from androgen precursors in adipose tissue.

Nevertheless, studies from Rochester, Minnesota,¹³ as well as elsewhere¹⁴ have shown an increase in fractures overall and hip fractures, specifically. Data from the Women’s Health Initiative Observational Study reveal an increased risk for fractures (Table 2).¹⁵ A number of other investigations including the Nurses’ Health Study,¹⁶ Iowa Women’s Health Study,¹² and the Study of Osteoporotic Fractures (SOF)^{17,18} have reported similar findings including an increase in peripheral fractures (especially lower limb as well as hip, but not usually vertebral fractures) despite a generally higher BMD in these patients. Interestingly, in the SOF there was an increased risk for falls that was greater in insulin users. Moreover, in the Nurses’ Health Study,¹⁶ hip fracture incidence was higher in insulin-treated T2DM patients. In the Health ABC Study,¹⁹ those who suffered a fracture had a higher incidence of diabetes complications (eg, neuropathy and cerebrovascular disease) and falls than those with T2DM who did not fracture. In addition, this study revealed that the BMD was lower in those who fractured compared to those who did not.

The associated risk factors and the precise mechanisms responsible for these observations are being actively explored. Evidence from the Mayo clinic study¹³ and a Canadian study²⁰ indicates that a longer duration of diabetes (>10 years) increases the relative risk estimates for the overall likelihood of a fracture. As with osteoporotic fractures in people without diabetes,

Table 2: The women’s health initiative (WHI) observational study: Type 2 diabetes and fracture in women¹⁵

	Age-adjusted RR (95%, CI)
Hip	1.41 (1.17, 1.70)
Proximal humerus	1.30 (1.07, 1.56)
Foot	1.44 (1.21, 1.71)
Ankle	1.34 (1.16, 1.55)
Spine	1.28 (1.04, 1.56)
Forearm	0.98 (0.84, 1.15)

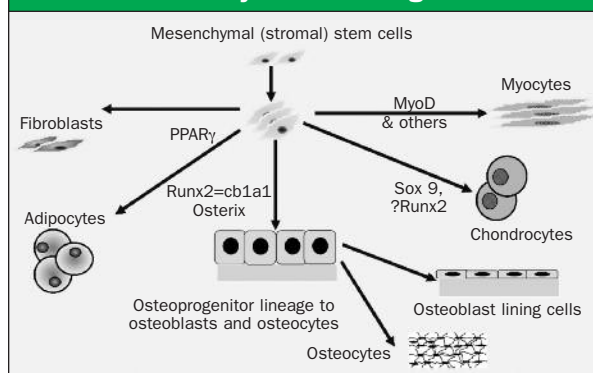
there is an ~2-fold increased risk for further fractures among people who have already experienced a fracture (the so-called fracture cascade).

PPAR γ activation and effects on bone

In vitro and preclinical (animal) studies

The transcription factor, peroxisome proliferator-activated receptor gamma (PPAR γ) is expressed in many tissues including bone marrow stromal cells, osteoblast and osteoclast precursors.²¹ The same mesenchymal stem cells can be differentiated into osteoblasts, adipoblasts, myoblasts, or chondroblasts depending on the appropriate stimulatory activity of different genes and transcription factors (Figure 4). *In vitro* studies have demonstrated that PPAR γ activation promotes adipogenesis at the expense of osteoblastogenesis.²² The net effect may be inhibition of bone formation and a consequent decrease in bone mass. Since PPAR signaling is an important determinant for the fate of pluripotent mesenchymal stem cells, the class of drugs that are agonists of PPAR γ , the thiazolidinediones (TZDs), have important actions on bone (Table 3). In fact, extensive experiments with rodents have demonstrated adverse effects on bone; in these animals, age appears to be an important determinant of the skeletal

Figure 4: Key genes for differentiation of mesenchymal cell lineages



PPAR γ = peroxisome proliferator-activated receptor γ

Table 3: Effect of PPAR γ agonists on bone cells, bone mass and architecture

1. Shift in flow of mesenchymal precursor cells from osteoblastic to adipogenic lineage
2. Increase in osteoblast and osteocyte apoptosis
3. Decreased osteoblast cell numbers and increased osteoclast cell numbers in rats
4. Decreased bone formation and slight increase in bone resorption biomarkers

Net effect: decreased bone formation and bone mineral density

effect. In younger adult rodents, decreased bone formation is seen with little effect on bone resorption; however, in older animals, TZDs increase osteoclast number and bone resorption. Partial gene knockout and transgenic murine models of altered PPAR γ signaling have elucidated the important role this transcription factor plays in skeletal metabolism.^{23,24} Animal data confirm the conclusion that PPAR γ activation is associated with decreased bone formation through a depletion of the pool of pluripotent stromal stem cells by diversion to adipogenesis.²⁵ Activation of osteoclastogenesis may also occur, especially in older animals. Moreover, TZD activation of PPAR γ in adipose tissue can influence production of various adipocytokines, including leptin and adiponectin that can have independent actions on bone.

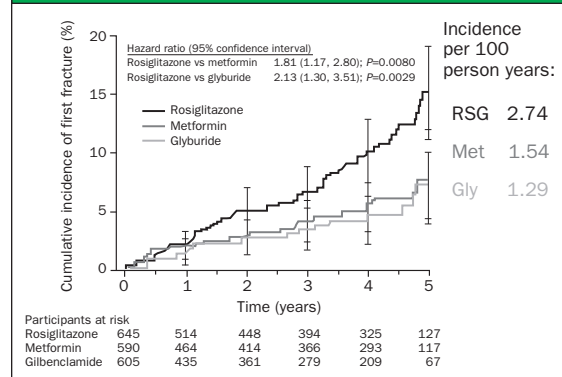
Effect of rosiglitazone and pioglitazone on bone mass and fracture incidence

Clinical studies

Recently, various clinical studies on the use of TZDs, including observational data, adverse event reports from diabetes randomized controlled trials (RCTs), and several small prospective controlled trials have demonstrated increased fracture incidence, as well as BMD and bone marker changes.²⁶ These negative effects have been identified for both rosiglitazone and pioglitazone.

The 4-year A Diabetes Outcome Progression Trial (ADOPT)²⁷ compared the durability of diabetes control with monotherapy using rosiglitazone, metformin, or glyburide, and revealed a significantly higher incidence of peripheral fractures (in women not men) among the rosiglitazone users compared with the other therapies (Figure 5). A similar increased fracture risk was identified for pioglitazone in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PRO-ACTIVE)²⁸ study. Indeed, interrogation of the TZD databases confirmed the increased fracture

Figure 5: Rosiglitazone increased fracture risk in women compared with metformin or glyburide²⁷



Reproduced with permission from Kahn SE, et al. *Diabetes Care*. 2008; 31(5):845-851. Copyright © 2008 The American Diabetes Association

incidence (primarily peripheral fractures, but also hip fractures depending upon the age of the population studied). The mechanism by which TZDs (both rosiglitazone and pioglitazone) may enhance bone loss has been explored in 3 recent RCTs of short duration. The studies examined premenopausal women with polycystic ovarian syndrome (PCOS)²⁹ and postmenopausal women with and without diabetes.³⁰ Biochemical marker analysis suggested decreased bone formation, and there were also significant declines in BMD by dual energy x-ray absorptiometry (DXA) at either the hip or spine, despite the short duration of the studies. If the rate of bone loss were to continue as measured, the predicted annualized rates of bone loss would be on the order of 4%-6% in the axial skeleton, greater than normally expected.

A nested case control analysis using the United Kingdom general practice research database (UKGPRD)³¹ provided further evidence that TZDs are associated with increased fractures and, moreover, in the older age group this was found in both men and women. The most recently published meta-analysis,³² reviewed 10 RCTs (of rosiglitazone and pioglitazone) and found a significantly increased risk of fractures overall (odds ratio [OR] 1.45; 95% confidence interval [CI], 1.18-1.79; $P<0.001$). In this analysis the increased fracture risk was again identified in women, but not in men; there was also a decrease in both lumbar spine and hip BMD. In these studies of diabetes populations taking thiazolidinediones, for those with newly diagnosed T2DM at a low risk of fractures, the number needed to harm (NNH) was 55 (95% CI, 34-103);²⁷ however, in older postmenopausal women with T2DM at a higher risk, the NNH was 21 (95% CI, 14-39).¹⁸

Conclusion

Since TZDs continue to be used to treat T2DM, there is a need for controlled studies to determine the long-term effects of these drugs.^{33,34} Thus far, there are no clinical trial data indicating a reduction of bone loss or a decrease in fracture risk with standard antiosteoporosis drugs used in T2DM patients treated with TZDs. Since there are no evidence-based medical guidelines to direct therapy, it may be prudent to avoid TZDs in those patients who have had fragility fractures or who are at a substantially increased risk for osteoporosis and fragility fracture. It is unknown whether the antiresorptive bisphosphonates would be an optimal treatment for a clinical situation where decreased bone formation is the principal problem.³⁵ By analogy it should be noted, however, that bisphosphonates have been used effectively in preventing and treating glucocorticoid-induced osteoporosis, another situation where decreased bone formation is a major problem. Until there are more definitive data, treatment of patients with TZDs, who are thought to be at increased osteoporotic fracture risk, should follow usual therapeutic guidelines.

References:

1. Dempster D. Anatomy and function of the adult skeleton. In: Favus M, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 6th ed. Washington, DC: American Society for Bone and Mineral Research (ASBMR); 2006:7-11.
2. Bone Biology Update: Bone Curriculum on the website of the American Society for Bone and Mineral Research (ASBMR): www.asbmr.org Accessed: March 18, 2009.
3. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423(6937):337-342.
4. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res*. 1996;11(3):337-349.
5. National and International Osteoporosis Foundation Websites: www.nof.org and www.iofbonehealth.org. Accessed: March 18, 2009.
6. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785-795.
7. Cummings S, Black DM, Rubin S: Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. *Arch Intern Med*. 1989;149(11):2445-2448.
8. 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(4):427-444.
9. de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int*. 2005; 16(12):1713-1720.
10. Brown SA, Sharpless JL. Osteoporosis: An under-appreciated complication of diabetes. *Clin Diabetes*. 2004;22(1):10-20.
11. Forsén L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag Health Survey. *Diabetologia*. 1999;42(8):920-925.
12. Nicodemus KK, Folsom AR; Iowa Women's Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. *Diabetes Care*. 2001;24(7):1192-1197.
13. Melton LJ 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. *J Bone Miner Res*. 2008;23(8):1334-1342.
14. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol*. 2007;166(5):495-505.
15. 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(9):3404-3410.
16. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care*. 2006;29(7):1573-1578.
17. Seeley DG, Kelsey J, Jergas M, Nevitt MC. Predictors of ankle and foot fractures in older women: the Study of Osteoporotic Fractures Research Group. *J Bone Miner Res*. 1996;11(9):1347-1355.
18. Schwartz AV, Sellmeyer DE, Ensrud KE, et al; Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab*. 2001;86(1):32-38.
19. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the Health, Aging, and Body Composition study. *Arch Intern Med*. 2005;165(14):1612-1617.
20. Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: A population based study. *Bone*. 2007;40(6):1595-1601.
21. Wahli W. PPAR gamma: ally and foe in bone metabolism. *Cell Metab*. 2008;7(3):188-190.
22. Lecka-Czernik B, Moerman EJ, Grant DF, Lehmann JM, Manolagas SC, Jilka RL. Divergent effects of selective peroxisome proliferator-activated receptor-gamma 2 ligands on adipocyte versus osteoblast differentiation. *Endocrinology*. 2002; 143(6):2376-2384.
23. Akune T, Ohba S, Kamekura S, et al. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. *J Clin Invest*. 2004;113(6):846-855.
24. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. *Nat Med*. 2007;13(12):1496-1503.
25. Botolin S, Faugere MC, Malluche H, Orth M, Meyer R, McCabe LR. Increased bone adiposity and peroxisomal proliferator-activated receptor-gamma2 expression in type I diabetic mice. *Endocrinology*. 2005;146(8):3622-3631.
26. Strotmeyer ES, Cauley JA. Diabetes mellitus, bone mineral density, and fracture risk. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(6): 429-435.
27. Kahn SE, Zinman B, Lachin JM, et al; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care*. 2008; 31(5):845-851.
28. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279-1289.
29. Glinborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP. 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*. 2008;93(5):1696-1701.
30. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR. 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*. 2007;92(4):1305-1310.

31. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch Intern Med.* 2008;168(8):820-825.
32. Loke YK, Singh S, Furberg CD. Long term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180(1):32-39
33. Grey A. Thiazolidinedione-induced skeletal fragility – mechanisms and implications. *Diabetes Obes Metab.* 2009;11(4):275-284.
34. Grey A. Skeletal consequences of thiazolidinedione therapy. *Osteoporos Int.* 2008;19(2):129-137.
35. Keegan THM, Schwartz AV, Bauer DC, Sellmeyer DE, Kelsey JL. Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women; the fracture intervention trial. *Diabetes Care.* 2004;27(7):1547-1553.

Abstract of Interest

Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes

VESTERGAARD P, REJNMARK L, MOSEKILDE L.

This case-control study sought to assess the effects of diabetes and its complications on the risk of fractures. There were 124,655 fracture cases and 373,962 age- and sex-matched controls. The main exposure was diabetes and its complications, and the main confounders were use of insulin and oral antidiabetic agents, presence of cardiovascular disease, and use of drugs for cardiovascular disease, along with a number of other confounders. In the crude analysis, diabetes and all complications was associated with a statistically significantly increased overall risk of fractures. The increase in risk of fractures was higher in type 1 diabetes (T1D) than in type 2 diabetes (T2D). However, after adjustment for confounders, the difference between T1D and T2D disappeared, and only diabetic kidney disease in T1D retained a significantly increased risk of fractures. There was a time dependency in the risk of fractures with an early increase at <2.5 years after diagnosis, followed by a decrease to the level of the background population from 2.5 to 5 years after diagnosis, and a limited increase in T1D but not T2D at >5 years after diagnosis. We conclude that diabetes, whether T1D or T2D, seems to carry an increased risk of fractures, and complications to diabetes except for diabetic kidney disease add little to the overall risk of fracture, perhaps pointing at a common risk factor linked to the high blood glucose levels, which may weaken bone strength.

Calcif Tissue Int. 2009;84(1):45-55.

Disclosure Statement: Dr. Josse has received research grants and/or speaking honoraria or serves on the Scientific Advisory Boards of the following companies: Merck Frosst, Procter & Gamble/Sanofi Aventis, Lilly, Novartis, GlaxoSmithKline, Servier, and Amgen.

Upcoming Scientific Meetings

31 July – 2 August 2009

5th Annual Diabetes Conference

College Station, TX

Contact: Coastal Bend Health Education Center

Telephone: 361-825-2804

Fax: 361-825-2809

6 – 7 August 2009

Diabetes and the Heart

Cleveland, OH

Contact: Cleveland Clinic Center for Continuing Education

Telephone: 800-238-6750 / 216-448-0770

Email: clevelandclinicmeded@ccf.org

6 – 10 August 2009

World Congress on Thyroid Cancer

Toronto, Ontario, Canada

Contact: Website: <http://www.thyroid2009.ca/>

9 – 12 September 2009

8th Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology

New York, NY

Contact: Pauline Bertrand, ESPE Secretariat, UK

Telephone: 44-0-01-454-642-208

Fax: 44-0-1-454-642-222

Website: <http://www.lwpes-espe2009.org/secondary.cfm?section=Welcome>

27 September – 1 October 2009

45th Annual Meeting of the European Association for the Study of Diabetes

Vienna, Austria

Contact: Website: <http://www.easd.org>

3 – 4 October 2009

Endocrinology 2009: New and Future Therapies for Obesity, Diabetes, and Cardiovascular Disease

Monterey, CA

Contact: Continuing Medical Education Office

Telephone: 916-734-5390 / 866-263-4338 / 866-CME-4EDU

Email: cmereg@ucdavis.edu

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Boehringer Ingelheim and sanofi-aventis

©2009 Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto, which is solely responsible for the contents. Publisher: **SNELL Medical Communication Inc.** in cooperation with the Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto. *Endocrinology Rounds* is a registered trade mark of SNELL Medical Communication Inc. All rights reserved. The administration of any therapies discussed or referred to in *Endocrinology Rounds* should always be consistent with the approved prescribing information in Canada. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.