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Diabetes and the Bone

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The Linkages Between Glucose and Bone Metabolism are an Active Area of Research

Bone itself has an effect on glucose metabolism through osteocalcin, a hormone that enhances insulin secretion and sensitivity, increasing β-cell mass and energy expenditure. *Esp*, an osteoblast-specific gene, inhibits osteocalcin function by favoring its carboxylation into the inactive form, blunting glucose handling [Lee NK et al. *Cell* 2007].

Insulin receptors in osteoblasts are substrates of *Esp*. In a series of animal studies, it was determined that inactivating insulin receptors in osteoblasts affects whole-body glucose metabolism. Indeed, insulin signaling in osteoblasts enhances bone resorption, and the acid pH that is generated by bone resorption activates osteocalcin via its decarboxylation. This regulatory mechanism controls whole-body glucose homeostasis in mice and humans [Ferron et al. *Cell* 2010].

The associations between glucose and bone metabolism likely contribute to the increased risk of bone fractures that is associated with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [Vestergaard P. *Osteoporosis Int* 2007; Vestergaard P et al. *Diabetologia* 2005]. However, the mechanisms of this increased risk appear to differ somewhat from the risk factors for osteoporosis and fracture in the general population.

For instance, patients with T1DM have far less bone density than would be expected in their bones and hips, while patients with T2DM have greater bone density than would be expected for their age [Vestergaard P. *Osteoporosis Int* 2007]. Yet, rather than the 20% to 25% reduced fracture risk that might be expected in T2DM, the actual risk is 70% higher. Alternatively, rather than the 42% increased risk of fracture that might be expected in patients with T1DM, the actual risk is increased nearly 6-fold [Janghorbani M et al. *Am J Epidemiol* 2007]. This suggests that bone quality, not just bone density, is related to the fracture risk in diabetes. Indeed, diabetes is a disease of low bone turnover [Hamada Y et al. *Bone* 2007].

Direct effects of diabetes that contribute to the higher incidence of fracture and lower bone turnover include hyperglycemia, with marked declines in serum markers of bone resorption and bone turnover occurring within 2 hours of ingesting glucose during an oral glucose tolerance test (OGTT) [Clowes JA et al. *J Clin Endocrinol Metab* 2003].

Increased calcium excretion (hypercalciuria) is observed early in the disease in patients with T1DM. These levels eventually moderate and return to normal, which could be related to improved control of hyperglycemia [McNair P et al. *Acta Endocrinol (Copenh)* 1979]. This is also reflected in fracture risk, which appears to be higher early in the disease [Vestergaard P et al. *Calcif Tissue Int* 2009]. The reduction in calcium levels typically results in higher levels of parathyroid (PTH) hormone. However, although PTH levels rise in patients with diabetes, the peak is far lower than in individuals without diabetes [Schwarz P et al. *Acta Endocrinol* 1992].

High blood glucose levels also affect the bone matrix, leading to the formation of advanced glycated end-products (AGEs), such as pentosidine, which results in lower bone biomechanical competence [Saito M et al. *Osteoporosis Int* 2010].

More indirect effects of diabetes on bone are related to high blood pressure. Studies in nondiabetic patients find results in greater urinary calcium excretion and bone loss; neuropathy, likely related to reduced physical activity; and macrovascular complications that reduce blood flow to bone [Cappuccio FP et al. *Lancet* 1999; Rix M et al. *Diabetes Care*

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1999; Vogt MT et al. *J Bone Miner Res* 1997]. Body mass index (BMI) is important in both diabetic and nondiabetic patients. The leaner body mass of patients with T1DM may help explain their lower bone density compared with those with T2DM, who tend to be heavier [Vestergaard P. *Osteoporosis Int* 2007]. Finally, increased PPAR-γ levels that result from chronic hyperglycemia, which suppresses osteoblast differentiation, promotes an adipocyte-like phenotype that results in less bone formation [Botolin S et al. *J Cell Biochem* 2006].

The Effects of Glucose-Lowering Agents on Bone

In addition to the mechanisms described above, certain glucose-lowering drugs can impact bone. Among the most studied are the thiazolidinediones rosiglitazone and pioglitazone. Both are independently associated with an increased risk of bone fracture in men and women with T2DM, with a doubling of the risk in women (Figure 1) [Kahn SE et al. *Diabetes Care* 2008; Aubert RE et al. *Diabetes Obes Metab* 2010; Home PD et al. *Lancet* 2009].

Figure 1. Rosiglitazone and Bone Fracture Risk in Women with T2DM.

Increased risk 82%

Increased risk 23%

RR:1.57 [1.26 - 1.97]*

	Women		Men		All	
	RSG (n=1078)	AC (n=1075)	RSG (n=1142)	AC (n=1152)	RSG (n=2220)	AC (n=2227)
All	124 (154)	68 (78)	61 (71)	50 (54)	185 (225)	118 (132)
Upper limb	63 (78)	36 (39)	23 (23)	19 (19)	86 (101)	55 (58)
Distal lower limb	47 (49)	16 (17)	23 (24)	11 (11)	70 (73)	27 (28)
Femur/hip	7 (8)	7 (7)	3 (3)	1 (1)	10 (11)	8 (8)
Spine	8 (8)	4 (4)	6 (6)	5 (5)	14 (14)	9 (9)
Pelvis	0	1 (1)	0	3 (3)	0	4 (4)
Other	11 (11)	10 (10)	14 (15)	15 (15)	25 (26)	25 (25)

Numbers are participants (events). Some participants had more than one fracture and in different areas of the body.
*p<0.001; RSG=rosiglitazone; AC=active control.

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This increased risk may be related to increased osteoclast activity rather than decreased osteoblast activity [Zinman B et al. *Lancet* 2010]. Animal and human studies suggest that these drugs may suppress osteoblast differentiation, decreasing osteoblastogenesis in human mesenchymal stem cells [Ali AA et al. *Endocrinology* 2005; Benvenuti S et al. *J Endocrinol Invest* 2007].

While a large case-control study of 2000 patients with T2DM who were followed for 4 years found a significant increase in bone fracture in patients who were using insulin, there was no reduction in bone mineral density [Monami M et al. *Diabetes Care* 2008; Stolk RP et al. *Bone* 1996]. The mechanism may be related more to the higher rate of hypoglycemia that occurs with insulin therapy, increasing the risk of falls [Schwartz AV et al. *Diabetes Care* 2002; Adami S. *Curr Med Res Opin* 2009].

Although hypoglycemia can also be induced by secretagogues, the risk is much lower than that observed with insulin, which may explain why insulin secretagogues are not associated with an increased risk of bone fracture [Vestergaard P et al. *Diabetologia* 2005; Monami M et al. *Diabetes Care* 2008]. Metformin also appears to have neutral effects on bone [Vestergaard P et al. *Diabetologia* 2005; Monami M et al. *Diabetes Care* 2008].

Meanwhile, the incretin-based therapies may exert some favorable effects on bone metabolism. Bone has receptors for glucagon-like peptide-1 (GLP-1). In animal models, GLP-1 receptor knockout mice exhibited higher osteoblast activity than wild-type mice, while even short-term treatment with the GLP-1 agonist exenatide stimulated the deposition of new bone in animal models of T2DM and insulin resistance [Nuche-Berenguer B et al. *Regul Pept* 2010]. Responsible mechanisms may be the ability of GLP-1 to prevent the differentiation of mesenchymal stem cells into adipocytes or stimulate thyroid C-cells, in turn stimulating increased calcitonin release and C-cell proliferation [Knudsen BL et al. *Endocrinology* 2010; Sanz C et al. *Am J Physiol Endocrinol Metab* 2010].

The dipeptidyl peptidase-4 (DPP4) inhibitors could affect bone both by increasing circulating GLP-1 levels and by increasing gastric inhibitory polypeptide, thus having a favorable effect on osteogenesis while decreasing bone resorption [Baggio LL et al. *Gastroenterology* 2007].

In conclusion, the low bone turnover in patients with diabetes may have implications for the treatment of osteoporosis in this population. The traditional therapy for osteoporosis is antiresorptive agents. However, this may contribute to further reductions in bone turnover. In addition, there seems to be a discrepancy between bone mineral density, as measured by dual-energy x-ray absorptiometry (DXA) scans, and bone biomechanical competence, especially in T2DM. Thus, it is unclear how DXA scans should be interpreted in diabetes. Finally, bone fractures should be considered among the treatment outcomes when choosing antidiabetic medications.