I recently read an interesting article in Diabetes Care (1) that showed that treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors could be associated with a reduced risk of bone fractures in type 2 diabetic patients. As the authors pointed out, since experimental data in animal models suggested that incretins such as glucagon-like peptide-1 (GLP-1) and gastric intestinal polypeptide (GIP) stimulate bone formation and increased bone density (2), it is conceivable that DPP-4 inhibitors could exert beneficial effects on the bone by increasing the levels of incretins. However, bone density is increased rather than decreased in type 2 diabetes (3). So, bone quality may be more important than bone density in defining the increased risk for fractures in type 2 diabetic patients.

There is accumulating evidence that advanced glycation end products (AGEs) could play a role in impaired bone quality in type 2 diabetes (4). Indeed, despite normal bone mineral density, bone mechanical properties were impaired in spontaneous diabetic rats, which coincided with the increased content of pentosidine, one of the well-characterized AGEs in the bone collagen (4). Serum pentosidine level was associated with the presence of vertebral fractures in postmenopausal type 2 diabetic women independent of bone density and other risk factors for osteoporosis (4). Urinary pentosidine level was also associated with both increased clinical fracture incidence and vertebral fracture prevalence in elderly patients with type 2 diabetes (4). Further, AGEs not only inhibited the proliferation and differentiation of osteoblasts but also induced activation of osteoblasts through the interaction with their receptor, RAGE (4). Mice lacking RAGE had increased bone density and biomechanical strength and decreased number of osteoclasts and bone resorptive activity (4). These observations suggest that the AGE-RAGE axis may be involved in reduced bone density as well, thus contributing to an increased risk of bone fractures in type 2 diabetes.

We have previously shown that GLP-1 and GIP reduce RAGE expression in endothelial and mesangial cells through the elevation of cyclic AMP levels and resultantly block the deleterious effects of AGEs in vitro (5). Further, we have recently found that treatment with vildagliptin, an inhibitor of DPP-4, suppresses the formation and accumulation of AGEs and reduces the expression levels of RAGE in thoracic aorta of type 2 diabetic rats (4). These observations suggest that the AGE-RAGE axis in the bone may also be a molecular target of DPP-4 inhibitors. It would be interesting to examine whether a reduced risk of bone fractures in type 2 diabetic patients with DPP-4 inhibitors is actually associated with increased bone density or correlated with decreased serum or urinary level of pentosidine. These data help us to understand how DPP-4 inhibitors could protect against bone fractures in type 2 diabetic patients.

SHO-IChi YAMAGISHI

From the Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan.

Corresponding author: Sho-ichi Yamagishi, shoichi@med.kurume-u.ac.jp.

DOI: 10.2337/dc11-2561 © 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

Acknowledgments—This work was supported in part by the Venture Research and Development Center of the Ministry of Education, Culture, Sports, Science and Technology to S.-Y.

No potential conflicts of interest relevant to this article were reported.

References
1. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes Care 2011;34:2474–2476
2. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132:2131–2157
3. 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;18:427–444
4. Yamagishi SI. Role of advanced glycation end products (AGEs) in osteoporosis in diabetes. Curr Drug Targets 2011;12:2096–2102
5. Yamagishi S, Matsu T. Pleiotropic effects of glucagon-like peptide-1 (GLP-1)-based therapies on vascular complications in diabetes. Curr Pharm Des 2011;17:4379–4385