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 COMMENTS AND  
 RESPONSES
 

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**Comment on:  
 Monami et al.  
 Dipeptidyl  
 Peptidase-4  
 Inhibitors and Bone  
 Fractures: A Meta-  
 analysis of  
 Randomized Clinical  
 Trials. *Diabetes Care*  
 2011;34:2474-  
 2476**

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) stimulated 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 with obesity, thus suggesting that DPP-4 inhibitors could play a protective role against vascular injury in type 2 diabetes partly by attenuating the harmful effects of the AGE-RAGE axis (5). Therefore, 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.

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