Dipeptidyl peptidase-4 inhibitors and prevention of bone fractures: Effects beyond glyemic control

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glycemic control in patients with type 2 diabetes by preventing degradation of two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are secreted from the intestine on ingestion of various nutrients, and enhance insulin secretion from pancreatic β-cells glucose-dependently[1]. Both incretin hormones show various biological functions in addition to their glucose-dependent insulinotropic action. Thus, DPP-4 inhibitors are expected to exert extra effects on various tissues and cell types. Among them, their effects on bones are of particular interest. A recent meta-analysis of randomized clinical trials comparing DPP-4 inhibitors with placebo or active comparator drugs in patients with type 2 diabetes suggested that treatment with DPP-4 inhibitors could be associated with a reduced risk of bone fractures[2].

Type 2 diabetes is associated with higher bone mineral density and, paradoxically, with increased fracture risk, presumably because of impaired bone quality that causes fragility fractures even when bone mass remains normal[3]. Duration of more than 10 years, presence of diabetic nephropathy, presence of diabetic neuropathy and high serum levels of pentosidine are shown to be risk factors for bone fractures[3]. One plausible mechanism of increased risk of bone fractures in patients with type 2 diabetes relates to chronic hyperglycemia, raising concentrations of advanced glycation end-products, such as pentosidine, that increases non-enzymatic collagen cross-linking and impairs bone quality. Furthermore, accumulating evidence shows negative impacts of antidiabetic drugs, thiazolidinediones, on bone turnover and bone fractures in patients with type 2 diabetes. However, so far, no oral antidiabetic drugs have been associated clinically with a reduction of bone fractures. Thus, the current finding on DPP-4 inhibitors by Monami *et al.* is highly promising despite some limitations, including short duration of the trials included, bone fractures being not principal end-points, and no discrimination between sexes and between pre- and postmenopausal women; and the Monami study provides a premise to initiate randomized, prospective, long-term clinical trials evaluating the effects of DPP-4 inhibitors on bone metabolism and bone fractures in patients with type 2 diabetes.

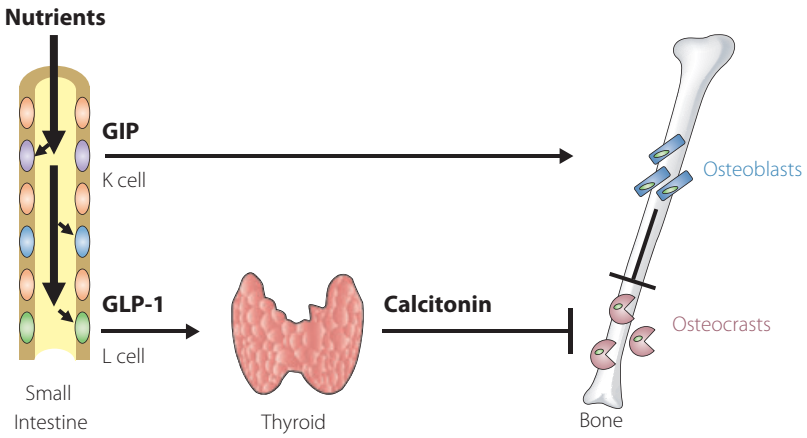

Figure 1 | The effects of two incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1), on bone metabolism. GIP binds to GIP receptors expressed on osteoblasts, thereby activating new bone formation. GIP also acts on osteocrasts, presumably through osteoblasts, to suppress bone resorption. In contrast, GLP-1 stimulates calcitonin secretion from the thyroid gland, which then suppresses bone resorption by osteocrasts.

The effects of GIP and GLP-1 on bone metabolism have been well characterized mainly in rodents (Figure 1)[1]. Investigations on GIP receptor-deficient mice and GIP transgenic mice showed that GIP increases bone mass by acting on osteoblasts to promote bone formation after meal ingestion, and inhibiting parathyroid hormone-induced bone resorption. Furthermore, GIP administration has been shown to attenuate ovariectomy-induced bone loss in rats. In contrast, studies on GLP-1 receptor-deficient mice showed that GLP-1 controls bone resorption, likely through a calcitonin-dependent pathway. Administration of GLP-1 receptor agonist exenatide has been shown to promote bone formation in normal and streptozotocin-induced diabetic rats, suggesting its insulin-independent action.

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Although these lines of evidence suggest an association of GIP and GLP-1 with bone turnover, the effects of GIP and GLP-1 on human bone turnover are largely unknown. A recent study showed that 44-week exenatide treatment did not affect bone mineral density in patients with type 2 diabetes[4]. As aforementioned, GLP-1 action on the bone is presumably mediated through calcitonin. A series of clinical trials on liraglutide, another GLP-1 receptor agonist, showed few changes in serum calcitonin levels in patients with type 2 diabetes, suggesting that GLP-1 might not play a role in human bone metabolism. Regarding GIP, Henriksen *et al.*[5] previously reported that postprandial reduction of bone resorption was not mediated by GIP, but GLP-2 – another intestinal hormone cosecreted with GLP-1. However, caution should be taken when interpreting their results, as they investigated the effects of subcutaneous single injections of native GIP that should be rapidly inactivated by DPP-4 before it reaches the bones. Therefore, further investigations are definitely required to understand GIP and GLP-1 actions on bone metabolism in humans.

Prevention of bone fractures could be the tip of the iceberg among potentially beneficial effects of DPP-4 inhibitors in patients with type 2 diabetes. It has been shown that DPP-4 inhibitors target not only two incretin hormones, GIP and GLP-1, but also other DPP-4 substrates, such as pituitary adenylate cyclase-activating peptide and stromal cell-derived factor-1α in patients with type 2 diabetes. Enhancement of these bioactive polypeptides could prevent progression of diabetic micro- and macrovascular complications independently of improvement in glycemic control. In the future, clinical trials with adequately powered, prospective, controlled relevant endpoints will clarify the effects of DPP-4 inhibitors beyond glycemic control.

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