JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Incretin action on bone: An added benefit?

Identification of the incretin hormones has led to revolutionary advances in the management of type 2 diabetes. There has been much recent excitement about the extrapancreatic actions of incretin hormones. Experimental studies have suggested that glucagon-like peptide-1 (GLP-1) could have beneficial effects on the cardiovascular system as well as the kidney, and this is currently an area of intense research. In addition, recent insights suggest that GLP-1 might have beneficial effects on the bone. GLP-1 receptor activation has been shown to lead to increased bone formation, suggesting possible beneficial effects of incretin therapies on reducing fractures[1]. Furthermore, glucose-dependent insulinotropic polypeptide (GIP) was found to regulate bone formation, with GIP-overexpressing mice having an increase in bone formation and a decrease in bone resorption[2], whereas the GIP receptor (GIPR) knockout mice have decreased cortical bone mass, decreased trabecular bone mass or compromised bone quality[3,4]. These studies support the existence of an entero-osseous axis, and potential beneficial effects of agents targeting the incretin pathway on bone health.

A recent study in humans provides further support for the role of GIP in regulating bone mass and fracture risk. To examine the relevance of GIP in mediating fracture risk, Torekov *et al.*[5] examined the association between a functional variant in the GIP gene, rs1800437, with incident fractures in a well-characterized prospective cohort. The variant, which causes a substitution of glutamate to glutamine at position 354 (Glu354Gln) in transmembrane domain 6, has been shown to lead to decreased receptor activity, and carriers of this variant have higher postprandial glucose levels with decreased insulin after oral glucose challenge, consistent with the decreased effect of GIP[6]. To examine the association between genetic variants in GIP with fracture risk, the authors genotyped rs1800437, and its proxy rs10423928, in 1,686 perimenopausal women from the Danish Osteoporosis Prevention Study, a multicenter, prospective, cohort study with detailed radiological assessment for fractures and bone mineral density (BMD) measurements at baseline, and after 5 and 10 years. Together, the two variants tag all genetic variation within the gene with minor allele frequency of at least 10% and $r^2 \geq 0.9$. With the two genotyped variants in tight linkage disequilibrium ($r^2 = 0.99$), the authors carried out the analysis for the functional variant, rs1800437. They found that carriers of the C allele had a trend towards lower BMD at the hip at baseline, adjusting for the covariates age, hormonal treatment and body mass index (BMI), and after 10 years, women carrying the C allele of rs1800437 had significantly lower BMD at the femoral neck and hip compared with carriers of the major G allele. There was no difference in BMD at the lumbar spine between women with the different genotypes. In a Cox regression analysis adjusting for age, hormonal treatment and BMI, women with the CC genotype had an increased risk of non-vertebral fractures during mean follow up of 16 years [hazard ratio 1.6 (95% confidence interval 1.0–2.5, $P < 0.05$)][5].

This well-conducted candidate gene study provided several novel insights on the role of GIP in bone metabolism. With 1,686 participants and long duration of follow up, the study was adequately powered for the study on changes in BMD. In addition to detailed documentation of incident fractures at the 5- and 10-year follow-up visits, data on fractures were also extracted from the Danish National Patient Registry, thereby providing a total follow-up duration of at least 16 years. There was also detailed categorization of different types of fractures, allowing separate analyses for vertebral vs non-vertebral fractures. The findings of increased risk of non-vertebral fractures among the CC carriers is consistent with results from the GIPR knockout mice, which suggests that GIPR deficiency has particularly detrimental effects on cortical bone. Previous studies using the GIPR knockout mice found increased trabecular bone mass, but decreased bone mineralization and strength at the tibia[4]. Conversely, bone mass, cortical thickness and strength were all reduced at mid-femur in the GIPR knockout mice[3].

This recent study adds to our understanding of the extrapancreatic effects of GIP (Figure 1). GIP plays a key role in modulating nutrient intake into adipose tissue, and therefore provides an important link between nutrient intake and obesity. Furthermore, GIP was found to induce inflammation and impaired insulin signaling in the adipocyte[7]. The emerging insights on the important role of GIP in regulating bone mass and strength provides another fascinating perspective on the pleiotropic effects of the incretin hormones, and potentially, pharmacological agents targeting this pathway. A previous genome-wide meta-analysis confirmed the association between a variant in GIPR, and reduced insulin secretion[6]. Findings from this current study suggest the effects of the variant on bone metabolism are probably greater than the effect on glucose metabolism. Interestingly, recent data suggests that incretin-based therapies could have beneficial effects on bone metabolism[8]. A meta-analysis of all randomized clinical trials of

*Corresponding author. Ronald Ma
Tel.: +852-26323307
Fax: +852-26373852
E-mail address: rcwma@cuhk.edu.hk
Received 19 July 2014; revised 30 July 2014; accepted 31 July 2014

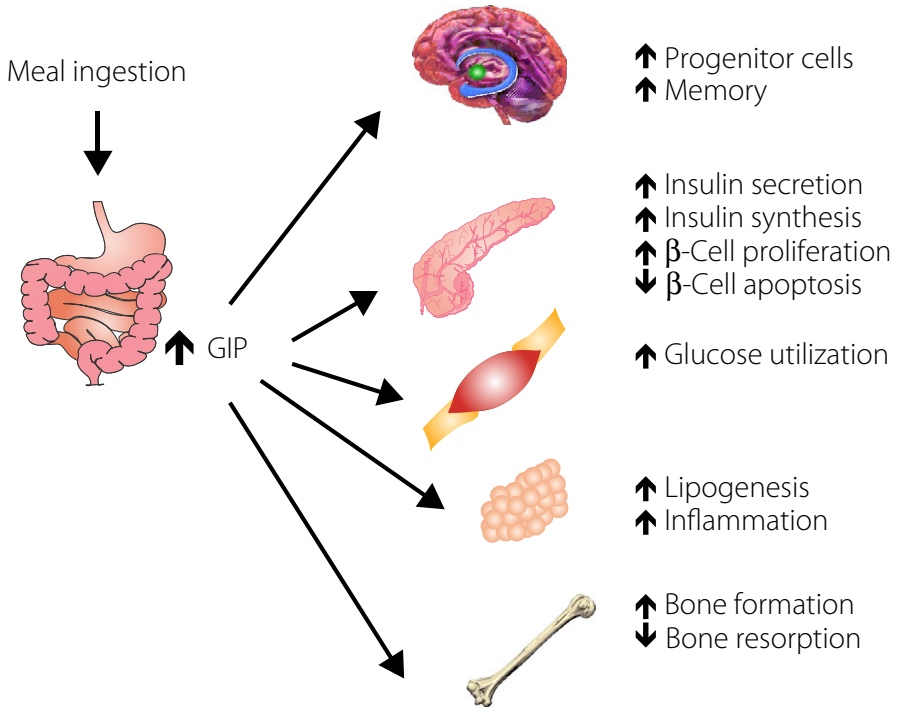

Figure 1 | Actions of glucose-dependent insulinotropic polypeptide (GIP) at its target organs. In addition to its well-known effects on pancreatic β-cell and insulin secretion, GIP has been found to have extrapancreatic effects on the brain, and enhancing memory, increasing glucose utilization in muscle, promoting lipogenesis and inflammation in adipose tissue, and increasing bone formation.

duration more than 24 weeks suggest that treatment with dipeptidyl peptidase-4 inhibitors was associated with a reduced risk of fractures[9]. Given the impairment of incretin receptors and their signaling in the diabetic state[10,11], and increased risk of fractures in both type 1 and type 2 diabetes, better understanding of the role of the incretin pathway in modulating bone metabolism would be an important area for further research.

ACKNOWLEDGMENTS

RCWM acknowledge funding support from the Research Grants Council Theme-based Research Scheme (T12-402/13N). RCWM has received speaker honoraria for educational lectures on diabetes from Bayer, Eli Lilly, Takeda, Nestle, Danone, Boehringer-Ingelheim, Pfizer, Wyeth and Astra-Zeneca during the past 4 years. RCWM has received research support for carrying out clinical trials on treatments for type 2 diabetes from Astra Zeneca and MSD.

Ronald C. W. Ma[1,2]*, Gang Xu[2,3]
[1]Department of Medicine and Therapeutics, [2]Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Shatin, New Territories, and [3]School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

REFERENCES

1. Yabe D, Seino Y. Incretin actions beyond the pancreas: lessons from knockout mice. *Curr Opin Pharmacol* 2013; 13: 946–953.
2. Bollag RJ, Zhong Q, Ding KH, *et al.* Glucose-dependent insulinotropic peptide is an integrative hormone with osteotropic effects. *Mol Cell Endocrinol* 2001; 177: 35–41.
3. Mieczkowska A, Irwin N, Flatt PR, *et al.* Glucose-dependent insulinotropic polypeptide (GIP) receptor deletion leads to reduced bone strength and quality. *Bone* 2013; 56: 337–342.
4. Gaudin-Audrain C, Irwin N, Mansur S, *et al.* Glucose-dependent insulinotropic polypeptide receptor deficiency leads to modifications of trabecular bone volume and quality in mice. *Bone* 2013; 53: 221–230.
5. Torekov SS, Harslof T, Rejnmark L, *et al.* A functional amino acid substitution in the glucose-dependent insulinotropic polypeptide receptor (GIPR) gene is associated with lower bone mineral density and increased fracture risk. *J Clin Endocrinol Metab* 2014; 99: E729–E733.
6. Saxena R, Hivert MF, Langenberg C, *et al.* Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet* 2010; 42: 142–148.
7. Nie Y, Ma RC, Chan JC, *et al.* Glucose-dependent insulinotropic peptide impairs insulin signaling via inducing adipocyte inflammation in glucose-dependent insulinotropic peptide receptor-overexpressing adipocytes. *FASEB J* 2012; 26: 2383–2393.
8. Ceccarelli E, Guarino EG, Merlotti D, *et al.* Beyond glycemic control in diabetes mellitus: effects of incretin-based therapies on bone metabolism. *Front Endocrinol (Lausanne)* 2013; 4: 73.
9. Monami M, Dicembrini I, Antenore A, *et al.* Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care* 2011; 34: 2474–2476.
10. Xu G, Kaneto H, Laybutt DR, *et al.* Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: possible contribution to impaired incretin effects in diabetes. *Diabetes* 2007; 56: 1551–1558.
11. Hodson DJ, Mitchell RK, Bellomo EA, *et al.* Lipotoxicity disrupts incretin-regulated human beta cell connectivity. *J Clin Invest* 2013; 123: 4182–4194.

Doi: 10.1111/jdi.12273