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Editorial

How the gut affects bone metabolism

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1. Introduction

The current epidemic of obesity and metabolic disease in the industrialized world has fueled considerable research into the human energy metabolism. Studies reported over the last two decades have established how satiety, hunger, glucose homeostasis, and energy expenditure are subtly modulated in the short-, medium-, and long-term by paracrine and endocrine feedback loops involving the gut, adipose tissue, liver, pancreas, and central and autonomic nervous systems. At the same time, bone tissue broke out of its mineral chains when research demonstrated its contribution to energy metabolism physiology. During human evolution, energy metabolism, locomotion, and reproduction combined to exert strong selection pressure, so that a very high level of organ function integration became crucial to ensure survival. Research into the brain-gut-bone triangle has shed light on the circadian variations in bone turnover, particularly their links to meals, which were discovered half a century ago. A more recent shift in concepts came from the identification of the gut microbiota as exerting major physiological effects, adding further complexity to the earlier paradigms.

This review is confined to the links connecting gastrointestinal peptides, the gut microbiota, and bone tissue. A discussion of gut serotonin falls outside the scope of this work. Furthermore, although leptin is expressed not only by adipocytes, but also in the stomach, we will not discuss its effects on bone. Other issues that are not raised here are the effect of hepatokines, particularly the pro-osteoblastic effect of FGF21 [1], and the influence of gastric acid on bone.

2. Gastrointestinal hormones

They comprise hormones that regulate food intake, such as peptide YY and ghrelin, and the incretins gastric inhibitor peptide (GIP) and glucagon-like peptides (GLP) 1 and 2 (Table 1). The effects of these peptides interact with those of adipokines (such as leptin and adiponectin) involved during changes in nutritional status; pancreatic hormones (insulin, amylin, and glucagon); and the complex network of brain peptides that control hunger and satiety, such as neuropeptide Y, melanocortins (proopiomelanocortin, POMC), melanocyte-stimulating hormone (αMSH), Agouti-related peptide, orexins, and neurotransmitters (e.g., dopamine, norepinephrine, and serotonin) [2] (Fig. 1). Gastrointestinal hormones have been identified as therapeutic targets for diabetes and obesity [3] in both pharmacological strategies and bariatric surgery.

2.1. Ghrelin

Ghrelin is chiefly produced by the oxyntic cells in the gastric fundus. It binds to the growth hormone secretagogue receptor (GHSR), which is expressed in the stomach, heart, lungs, pancreas, gut, kidneys, gonads, adipose tissue, hypothalamus, and bone. Ghrelin is found as acyl-ghrelin, the only active form, and des-acyl-ghrelin. Ghrelin increases appetite when the stomach is empty, and its serum levels peak just before meals. When the stomach fills, peptide YY, cholecystokinin, and glucagon-like peptide-1 (GLP-1) are released and inhibit the secretion of ghrelin. Serum ghrelin levels are low in obese patients and increase after a period of dieting responsible for weight loss. Nevertheless, male and female mice that lack ghrelin or GHSR exhibit normal growth, food intake, and responses to underfeeding or overfeeding; their body weight is similar to that of wild-type mice, and their bone phenotype is normal [4].

In early studies, administering exogenous ghrelin increased both growth and bone mass by influencing growth hormone (GH) release and activating the GH-IGF-1 axis. Cultured osteoblasts (primary cultures and cell lines) express transcripts of GHSR1a and ghrelin, and both proteins are found on bone surfaces [5]. When exogenous ghrelin is given to normal or GH-deficient rats in doses that do not cause weight gain, bone mineral density (BMD) increases. In vitro, ghrelin suppresses osteoclastogenesis and enhances osteoblast proliferation and differentiation [6], with variations in the magnitude of these effects across models. These data support a direct effect of ghrelin on bone, independent from GH. In a recent study in rats, ghrelin infusion into the cerebral

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Table 1
Recapitulation of some of the physiological and bone effects of the main gastrointestinal hormones.

	Site of production	Trigger for release	Main metabolic and digestive effects	Effects on bone
Gastrin	G-cells in the gastric antrum and duodenum	Distension of the stomach by meals	↑↑ satiety ↑ secretion of acid, pancreatic juice, and bile	?
Ghrelin	Gastric oxyntic (parietal) cells	Empty stomach	↑ hunger and food intake ↑ gastric emptying ↑ GH ↓ insulin	Anabolic Anti-catabolic
Cholecystokinin (CCK)	I-cells in the duodenum	Fatty acids or amino acids in the duodenum	↑ satiety ↓ gastric emptying ↑ gallbladder contraction, secretion of pancreatic juice	?
Secretin	S-cells in the duodenum	Low pH in the duodenum	↑ insulin ↓ gastric acid	?
Amylin	β cells in the pancreas	↑ in blood glucose	↓ food intake (effect on the brain)	Anabolic Anti-catabolic
Insulin			↓ blood glucose	Anabolic
Preptin			↑ insulin	Anabolic
Pancreatic polypeptide (PP)	PP cells in the pancreas and bowel	High-protein meal	↑ satiety ↑ insulin ↑ secretion of pancreatic juice and hormones	?
Glucagon	α cells in the pancreas	↓ in blood glucose	↑ satiety anti-insulin effect	?
Peptide YY	L-cells in the bowel		↑ satiety ↓ gastric emptying	Controversial
Glucagon-like peptide -1 (GLP-1)			↑ satiety ↑ insulin	Anabolic?
Glucagon-like peptide -2 (GLP-2)			↓ gastric emptying	Anti-catabolic
Oxyntomodulin	K-cells in the bowel	Nutrients in the gastrointestinal tract	↑ satiety ↑ energy expenditure, agonist of receptors for glucagon and GLP-1	?
Glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide, GIP)			↑ insulin ↑ postprandial glucagon ↑ fatty acid storage	Anabolic?
Vasoactive intestinal polypeptide (VIP)	Enteric nervous system and efferent parasympathetic branches	Stimulation of the vagus nerve	↑ splanchnic vasodilation ↑ gastric acid ↑ pancreatic hormone release ↑ gastrointestinal tract ↑ hypothalamus	?

↑: increase; ↓: decrease.

ventricles increased bone mass via an effect that was independent from appetite and weight gain [7].

Epidemiological studies of correlations linking serum ghrelin levels to bone mass yielded dissonant results [8]. In a comparison of obese children and healthy controls, serum acyl-ghrelin correlated negatively with whole-body bone mass in healthy controls, whereas serum des-acyl-ghrelin correlated positively with whole-body bone mass in the group with obesity [9]. A 4-hour intravenous ghrelin infusion induced no significant changes in bone turnover markers in post-gastrectomy patients or healthy controls [10]. In contrast, in healthy adults aged 60 to 81 years, 1 year of treatment with an oral ghrelin mimetic caused a small increase in BMD compared to the placebo [11]. Thus, ghrelin exerts complex influences on bone that are due to both central and peripheral effects and may depend on gender and nutritional status.

2.2. Peptide tyrosine-tyrosine (peptide YY)

The precursor of peptide YY (PYY) is produced by L-cells in the distal ileum, colon, and sigmoid. Cleavage by the enzyme dipeptidase-4 (DPP4) releases the active circulating form PYY3-36. PYY production increases during meals. PYY suppresses appetite, thereby limiting the size of the meal and the amount of calories ingested. In the brain, PYY inhibits the effect of neuropeptide Y by binding to the Y2 receptor. Patients with anorexia have elevated serum PYY levels. In vitro, PYY activates a signaling pathway in osteoblasts that express the Y1 receptor.

PYY-deficient mice exhibit similar body weight and growth to those in wild-type mice until 14 weeks of age. The effects of PYY knockout are controversial. In one study, $PYY^{-/-}$ mice had lower whole-body BMD with a marked decrease in trabecular bone mass compared to wild-type littermates, in both genders and at ages ranging from 2 to 9 months [12]. However, PYY deficiency has also been reported to increase bone mass in both male and female mice as a result of an osteoblast-stimulating effect. Females with PYY overexpression have smaller bones and lower bone mass with both a decrease in bone formation and an increase in bone resorption.

2.3. Incretins

Incretins are peptides secreted by endocrine cells in the small bowel in response to the ingestion of carbohydrates. Incretins act on the pancreas to modify the release of insulin and to inhibit the release of glucagon.