Postprandial Gut Hormones

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Gut-derived hormones have been suggested to play a role in bone homeostasis following food intake, although the associations are highly complex and not fully understood. In a randomized, two-day cross-over study on 14 healthy individuals, we performed postprandial time-course studies to examine the associations of the bone remodeling markers carboxyl-terminal collagen type I crosslinks (CTX) and procollagen type 1 N-terminal propeptide (P1NP) with the gut hormones glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) using two different meal types—a standardized mixed meal (498 kcal) or a granola bar (260 kcal). Plasma concentrations of total GIP, total GLP-1, total PYY, CTX, and P1NP were measured up to 240 min after meal intake, and the incremental area under the curve (iAUC) for each marker was calculated. The iAUC of CTX and P1NP were used to assess associations with the iAUC of GIP, GLP-1, and PYY in linear mixed effect models adjusted for meal type. CTX was positively associated with GIP and GLP-1, and it was inversely associated with PYY (all $p < 0.001$). No associations of P1NP with GIP or GLP-1 and PYY were found. In conclusion, the postprandial responses of the gut hormones GIP, GLP-1, and PYY are associated with the bone resorption marker CTX, supporting a link between gut hormones and bone homeostasis following food intake.

bone markers gut hormones bone metabolism CTX P1NP

1. Introduction

Bone remodeling is a highly dynamic process that takes place throughout life and helps maintain the skeleton [1]. Circulating bone remodeling biomarkers can be used to assess bone metabolic status [2]. Carboxyl-terminal collagen type I crosslinks (CTX) is an indicator of bone resorption, where osteoclasts breaks down the bone tissue, whereas procollagen type 1 N-terminal propeptide (P1NP) is an indicator of bone formation, where osteoblasts build up the bone tissue [3][4]. Studies have shown a circadian pattern for bone remodeling, with high bone resorption taking place during nighttime and high bone formation taking place during daytime, correlating with the highest CTX concentration in the morning after an overnight fast [5][6]. The bone remodeling marker levels also change acutely following food intake, where CTX is reduced and P1NP is increased, thus reflecting increased bone formation [7][8].

The gut hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 and 2 (GLP-1/2) are secreted postprandially by the intestinal K and L cells, respectively [9]. Accumulating evidence suggests that these hormones and especially GIP are involved in bone remodeling [10][11]. Recent studies have shown that the intravenous infusion of GIP acutely decreases CTX plasma levels, which is suggestive of increased bone formation [12][13]. Treatment with the GLP-1 receptor agonist liraglutide has been shown to increase P1NP levels

and to maintain bone mineral density in obese women after weight loss, suggesting a positive effect of GLP-1 on bone formation [14]. Interestingly, infusion with GLP-1 acutely suppresses circulating CTX levels similar to GIP, but when co-infused, GLP-1 plus GIP seem to have partially synergistic effects on CTX [14]. The appetite-inhibiting hormone Peptide YY (PYY) is co-secreted postprandially from the intestinal L-cells with GLP-1/2 and is believed to mainly have bone resorptive effects [6]. Thus, gut hormones seem to represent an important link between food intake and bone homeostasis; however, the complexity of the associations between different gut hormones and bone turnover markers following food intake remains elusive.

In this study, we aimed to further investigate the associations between the bone remodeling markers CTX and P1NP and the gut hormones GIP, GLP-1, and PYY following the intake of two types of meals in healthy individuals.

2. Development and Findings

In this study, we investigated whether the postprandial plasma levels of the gut hormones GIP, GLP-1, and PYY are associated with the levels of the bone remodeling markers CTX and P1NP following the intake of two different meal types—a standardized mixed meal or a granola bar. We found associations between CTX and all three gut hormones, whereas no associations were found for P1NP.

Our results from the mixed effect models showed that GIP and GLP-1 were positively associated with CTX, whereas PYY was inversely associated with CTX. These findings are in accordance with previous studies reporting a relationship of GLP-1 and especially GIP with bone turnover markers, including CTX [11][13][15]. Our study thus confirms gut hormones as likely critical bone turnover regulators, thereby representing a link between food intake and bone homeostasis. As opposed to other studies, which primarily used GIP and/or GLP-1 infusions [11][13][15], we used two different mixed meal types containing different amounts of calories: 260 kcal for granola bar vs. 498 kcal for standardized mixed meal. The combined association analysis of both mixed meal types is a strength of our study. Another strength in this study is the repeated measurements in the same individual.

Postprandial GIP plasma levels correlate with bone remodeling, and recent studies have examined whether the intravenous administration of GIP or a GIP receptor antagonist affects the postprandial plasma levels of bone turnover markers. The studies reported that infusion with GIP caused a decrease in CTX and an increase in P1NP [12][13][15], whereas GIP receptor antagonism partly reversed the postprandial decrease in CTX [15]. Another study reported that GIP in combination with high plasma glucose acutely lowers CTX [16]. GIP may therefore be the single most important gut hormone modulator of bone turnover following food intake, but more studies are needed to fully clarify and discriminate between the individual effects of different gut hormones in regulating bone homeostasis.

If gut hormones constitute a link between food intake and bone homeostasis, gut hormones may directly affect bone turnover via binding to receptors on the surface of the osteoblasts and/or osteoclasts. In line with this notion, both bone and osteoblast- and osteoclast-derived cell lines express the GIP receptor (GIPR), supporting the notion that GIP could have direct bone remodeling effects [6][17][18][19]. It remains to be established if osteoblasts and osteoclasts express the GLP-1 receptor, as opposing data exists [18]. However, as GLP-1 stimulates bone marrow

stromal cell differentiation into osteoblasts, GLP-1 may promote bone formation indirectly by increasing the number of osteoblasts from marrow stromal cells [20]. Hence, opposed to the effect of GIP, which may directly stimulate osteoblast activity and, hence, bone formation, GLP-1's effect on osteoblasts is mainly dependent on the formation of new cells, which is unlikely to have an acute bone formation effect. In this way, GLP-1 may set the scene for more pronounced and direct effects exerted by other bone remodeling hormones such as GIP, although this is purely speculative.

We did not observe any postprandial changes in the P1NP levels following the intake of either meal type and found no statistically significant associations between the iAUC for P1NP and the three gut hormones. While some studies reported decreased P1NP levels after food ingestion, which is indicative of decreased bone formation [21][22][23], others also found a lack of postprandial P1NP changes following oral glucose tolerance testing or GIP infusion [11][15]. In these studies, however, the meals consisted of more calories (up to 2150 kcal) compared to the number of calories in the present study (260/498 kcal). This may indicate that more calories or a higher food volume is needed to cause a decrease in P1NP [21][22][23].

We did not measure bone markers other than CTX and P1NP, such as osteocalcin, in the current study. However, while some animal studies suggest a link between gut hormones and osteocalcin, there seems to be a general lack of clinical evidence for associations between gut hormones and osteocalcin [6][24].

The inverse association between CTX and PYY suggests that PYY may play a role in postprandial bone turnover via catabolic effects on bone. The idea that PYY is a negative regulator of osteoblastic bone formation is supported by studies in PYY receptor knockout mice, which demonstrated accelerated and increased bone growth and mass [25][26]. Studies in humans also previously reported inverse relationships between bone formation and PYY, thereby further linking PYY to bone homeostasis [27][28][29][30].

The limitations of our study include the small sample size (n = 14), the sex distribution skewing towards female, and that both pre- and postmenopausal women are included. Although these limitations may hamper our study in terms of generalizability, we believe our identified associations between postprandial gut hormones and bone markers add to the current knowledge of the gut–bone axis. Larger and more equally distributed studies should be performed to further elucidate the associations observed in our study. We believed the use of two different meal types makes our study somewhat more representative and physiologically relevant compared to most other studies investigating associations between gut hormones and bone markers. Another strength of our study is that we included multiple timepoints up to 240 min after food intake, allowing us to perform iAUC association analyses, which contrasts with many other studies, which only examined a single or a few postprandial timepoints. Hence, the current study may better reflect the normal postprandial physiology of the gut–bone axis.

3. Conclusions

Our study supports an association between gut hormones and the bone marker CTX after food intake, thereby adding to the evidence that gut hormones play an important role in the postprandial signal for bone formation when

energy and nutrient supply are abundant.

References

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