Current Osteoporosis Reports (2023) 21:21–31
https://doi.org/10.1007/s11914-022-00767-2

BONE AND DIABETES (A SCHWARTZ AND P VESTERGAARD, SECTION EDITORS)

The Gut-Bone Axis in Diabetes

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Accepted: 3 November 2022 / Published online: 28 November 2022

Abstract

Purpose of Review To describe recent advances in the understanding of how gut-derived hormones regulate bone homeostasis in humans with emphasis on pathophysiological and therapeutic perspectives in diabetes.

Recent Findings The gut-derived incretin hormone glucose-dependent insulinotropic polypeptide (GIP) is important for postprandial suppression of bone resorption. The other incretin hormone, glucagon-like peptide 1 (GLP-1), as well as the intestinotrophic glucagon-like peptide 2 (GLP-2) has been shown to suppress bone resorption in pharmacological concentrations, but the role of the endogenous hormones in bone homeostasis is uncertain. For ambiguous reasons, both patients with type 1 and type 2 diabetes have increased fracture risk. In diabetes, the suppressive effect of *endogenous* GIP on bone resorption seems preserved, while the effect of GLP-2 remains unexplored both pharmacologically and physiologically. GLP-1 receptor agonists, used for the treatment of type 2 diabetes and obesity, may reduce bone loss, but results are inconsistent.

Summary GIP is an important physiological suppressor of postprandial bone resorption, while GLP-1 and GLP-2 may also exert bone-preserving effects when used pharmacologically. A better understanding of the actions of these gut hormones on bone homeostasis in patients with diabetes may lead to new strategies for the prevention and treatment of skeletal frailty related to diabetes.

Keywords Bone · C-terminal telopeptide of type I collagen (CTX-I) · Diabetes · Glucagon-like peptide 1 (GLP-1) · Glucagon-like peptide 2 (GLP-2) · Glucose-dependent insulinotropic peptide (GIP)

Introduction

Diabetes is characterized by hyperglycaemia and associated with diabetic complications that can be prevented by treatment [1–3]. Although fractures are not considered a classical complication, both type 1 diabetes (T1D) and type 2 diabetes (T2D) are associated with increased risk of fractures [4]. Patients with T1D are characterized by decreased bone mineral density (BMD) whereas, paradoxically, BMD seems to be increased in T2D [4–6]. The dynamic processes controlling bone homeostasis, i.e., the balance between bone formation and bone resorption and the resulting bone structure, are regulated in a diurnal pattern with bone resorption dominating through the night and bone formation dominating during daytime [7, 8, 9•].

Suppression of bone resorption during daytime is related to food intake and several hormones secreted from the gastrointestinal tract after a meal may contribute to this phenomenon. The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are best known for their gluco-regulatory effects and, for GLP-1, its involvement in appetite regulation [10, 11], while glucagon-like peptide 2 (GLP-2), co-secreted with GLP-1, is known to maintain gut mucosal integrity via an intestinotrophic effect (stimulation of intestinal mucosa growth) [12]. In recent years, evidence that some of these hormones (GIP and GLP-2) have suppressive effects on bone resorption have led to the idea of an endocrine gut-bone axis playing an important role for bone health [13–16]. The insulinotropic and glucose-lowering effects of GIP and GLP-1 together with GLP-1's appetite-

This article is part of the Topical Collection on *Bone and Diabetes*

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reducing effect have led to the development of incretin-based drugs for the treatment of T2D and obesity [17], and the intestinotrophic effect of GLP-2 has been exploited in the development of GLP-2 analogues for the treatment of short bowel syndrome [18]. Little is known about the potential link between gut-derived hormones and diabetic bone fragility. Also, no gut hormone-based drugs for bone-related disorders are currently available and effects of existing gut hormone-based drugs on bone health have only recently started to emerge.

Here, we review findings describing how the gut hormones GIP, GLP-1 and GLP-2 are involved in bone physiology and potentially may be implicated in the bone pathophysiology of diabetes. Also, we address the effects of gut hormone-based drugs on bone health and provide a discussion of the potential of such drugs for the future treatment of bone-related disorders.

Literature Search

A literature search was conducted in PubMed using search strings including the terms bone, osteoporosis, fracture, diabetes, gut hormones, incretin hormones, GLP-1, GLP-2, and GIP. Only English language articles were selected. Online searches were also conducted in relevant congress abstract compilations and hand search of the reference lists in relevant articles were reviewed for additional literature.

Bone Remodelling—Involvement of the Gut

The bones are continuously remodelled by an ongoing process of degradation (resorption) and regeneration (formation), which must be in balance in order to avoid osteopenia or excess bone formation and is regulated by several factors such as mechanical stress, hormones, and cytokines [19, 20]. Several circulating markers of these processes, so-called bone turnover markers (BTM), exist. The two most commonly used BTMs are bone-specific fragments of collagen: N-terminal propeptide of type I procollagen (P1NP) reflecting bone formation and C-terminal telopeptide of type I collagen (CTX-I) reflecting bone resorption [21]. While bone formation, as assessed by P1NP, remains relatively stable during the day, CTX-I-assessed bone resorption exhibits a circadian variation with a peak in the morning followed by nadir in the afternoon [9•]. This variation is at least partly mediated by food intake, which suppresses levels of CTX-I robustly compared to fasting and intravenous glucose [7, 8]. Clowes et al. showed that oral glucose intake (75 g oral glucose tolerance test (OGTT)) induced a ~50% decrease in CTX-I after 2 h, and this effect was completely abolished when subjects received octreotide, a long-acting analogue of somatostatin reducing the secretion of many gastrointestinal hormones as well as insulin secretion from the pancreas [13]. These findings indicate that the postprandial suppression of bone resorption may be caused by gut-derived hormones, directly or via their insulinotropic effects (insulin also exerts a suppressive effect on bone resorption), a notion that subsequently has been substantiated by several lines of evidence [22, 23]. During intravenous isoglycaemic glucose infusion (IIGI) mimicking the glucose excursion observed during an OGTT, CTX-I declines as seen during fasting, i.e., less than during OGTT [22, 24]. This emphasizes that factors from the gut rather than the prevailing plasma glucose concentration drive the postprandial suppression of bone resorption. Due to OGTT-induced release of GIP and GLP-1, both potent insulinotropic hormones, oral ingestion of glucose causes greater insulin secretion compared to during IIGI (a phenomenon known as the incretin effect) [25–27], which may explain part of the difference in bone resorption observed during OGTT and IIGI [28, 29]. Nevertheless, several findings (reviewed below) support insulin-independent effects of gut hormones on suppression of bone resorption [30, 31••].

Effects of the Gut Hormones GIP, GLP-1, and GLP-2 on Bone Metabolism

In the following, the separate effects of the gut hormones GIP, GLP-1, and GLP-2 in normal physiology with focus on recent findings are reviewed. See Fig. 1 for an overview of the proposed effects of GIP, GLP-1, and GLP-2 on postprandial bone metabolism.

GIP

GIP is secreted into the circulation by enteroendocrine K cells in the small intestine in response to nutrients in the lumen of the gut. Its actions are mediated through the GIP receptor expressed in alpha, beta, delta, and PP (gamma) cells of the endocrine pancreas, bone tissue, blood vessels, and the heart [11]. Endogenous GIP potently stimulates insulin secretion in a glucose-dependent manner contributing to the incretin effect [27, 32]. In addition to its strong insulinotropic effect at elevated plasma glucose levels, exogenous GIP stimulates release of glucagon during euglycaemia and hypoglycaemia, respectively [33, 34]. In some rodent studies, GIP has been shown to reduce food intake and appetite [11]. However, these effects have not been confirmed in humans and the role of GIP in human body weight regulation is unsettled and debated [11, 35–37]. Furthermore, GIP increases adipose tissue blood flow and hereby increases triacylglycerol deposition to the subcutaneous adipocytes in healthy individuals [38–40]. Lastly, recent data suggest that endogenous GIP may facilitate intestinal lipid uptake during a meal [41].

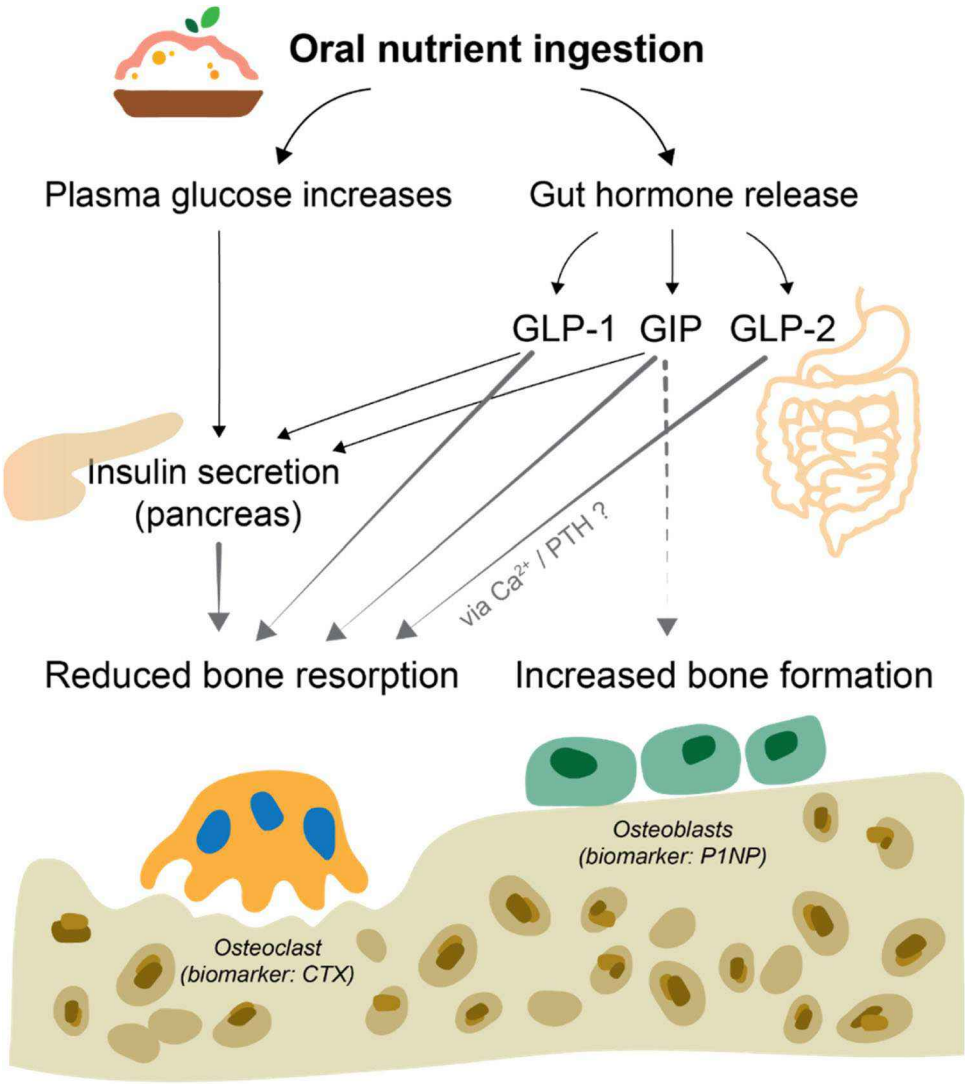

Fig. 1 Suggested pathways mediating postprandial regulation of bone metabolism. In the hours after nutrient stimulation of the gut, bone resorption decreases while bone formation is (largely) unaffected. The main driver of this postprandial suppression of bone resorption seems to be the gut-derived hormone GIP acting directly on bone cells, and GLP-2 which may suppress PTH (due to direct effects of GLP-2 on the parathyroid gland and/or increased Ca^{2+} uptake from the intestine mediated by GLP-2). GLP-1 may indirectly decrease bone resorption by potentiating insulin secretion or directly on osteoclasts. Ca^{2+}, calcium ion; CTX-I, C-terminal telopeptide of type I collagen; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; P1NP, N-terminal propeptide of type I procollagen; PTH, parathyroid hormone

GIP is an important factor in the gut-bone axis linking nutrient intake to the bone remodelling process [8, 13, 42]. Studies in healthy individuals have shown that acutely administered GIP in pharmacological doses inhibits CTX-I-assessed bone resorption by ~30–50% after 90 min [43–46]. Similar findings have been observed in C-peptide negative patients with T1D suggesting that the effect of GIP on bone resorption is not mediated through GIP-induced insulin secretion [31••]. Further, exogenous GIP has been observed to cause a small and transient increase in bone formation after ~30 min [31••, 43, 47]. GIP receptors are present in osteoclasts and osteoblasts supporting a direct effect of GIP [44]. In line with this notion, GIP increases intracellular cAMP levels in osteoblast-like cells causing increased bone formation in vitro [48]. Supporting the involvement of GIP in bone health, genetic variants of the GIP receptor with decreased receptor activity have been associated with lower BMD and increased fracture risk [49, 50]. In a physiological setting, using a GIP receptor antagonist, endogenous GIP could be shown to inhibit bone resorption in healthy individuals [30, 51]. Taken together, these studies support that GIP is a key hormone in the endocrine gut-bone axis (Fig. 1).

GLP-1

GLP-1 is a potent insulinotropic and anorexigenic gut hormone secreted by enteroendocrine L cells found in both the small and large intestines and its actions are mediated through GLP-1 receptors localized in beta cells (in the islets of Langerhans), blood vessels, the heart, and the brain [52]. These receptors are targeted by an effective class of drugs, GLP-1 receptor agonists (GLP-1RA), used in the treatment of diabetes and obesity [17, 53].

A clinical trial [54] and many animal models [55] have suggested that GLP-1RAs may have bone protective effects. However, the acute suppressive effects of GLP-1 on bone resorption are inconsistent. About 90–120 min after subcutaneous administration of native GLP-1 reaching pharmacological

levels, a decrease of about ~20% in CTX-I was observed in healthy participants [56]. In another study, GLP-1 in pharmacological doses caused a decline in CTX-I levels by ~65% when infused intravenously during an IIGI in overweight men without diabetes [47]. This was comparable to the decline during an OGTT and greater than the decline seen during IIGI with infusion of placebo (saline) (~28%) [47]. As high levels of insulin have been shown to suppress bone resorption [29], these findings could be due to the potent insulinotropic effect of GLP-1. In the abovementioned experiments, endogenous insulin levels were indeed high due to the combination of intravenous glucose administration and supraphysiological levels of GLP-1. In patients with T1D, exogenous GLP-1 reaching pharmacological concentrations did not have an effect on bone resorption [31••], supporting that effects of GLP-1 on bone resorption are mediated via GLP-1's insulinotropic effect. Using a GLP-1 receptor antagonist, exendin(9-39)NH_2, the suppressive effect of GLP-1 on bone resorption during an OGTT and a mixed meal was found to be negligible in healthy men [27]. Exendin(9-39)NH_2 causes compensatory L cell secretion, including release of GLP-2 [57], which could lead to decreased bone resorption (reviewed below), but levels of GLP-2 were not reported. Taken together, acute and short-term effects of GLP-1 on bone resorption seem to be indirectly mediated via insulin (at high or supraphysiological concentrations) and play a minor role during OGTT or mixed meal test.

GLP-2

GLP-2 is co-secreted with GLP-1 and derived from the same propeptide, proglucagon, but does not stimulate insulin secretion [58, 59]. The actions of GLP-2 are mediated through the GLP-2 receptor primarily found in the gastrointestinal tract and the gallbladder [12] and, importantly, GLP-2 stimulates growth of intestinal mucosa which is used therapeutically for treatment of small bowel syndrome [18].

Several studies support that exogenous GLP-2 suppresses bone resorption [14, 43, 44, 46, 60–66]. Acute administration of GLP-2 in pharmacological concentrations suppresses CTX-I to the same extent (by ~50%) as exogenous GIP but with a later nadir [43, 46]. Thus, GLP-2 is potentially a mediator of the postprandial suppression of bone resorption, but this has not yet, to our knowledge, been investigated in a setting with physiological hormone levels, e.g., using an antagonist of the GLP-2 receptor or infusions of GLP-2 targeted to reach physiological rather than supraphysiological levels. After administration of GLP-2 over weeks to months, the suppressive effect of GLP-2 on bone resorption is sustained [60, 61, 67] and accompanied by increased BMD [60, 67]. This implicates that GLP-2 receptor agonism may be a viable treatment modality for osteoporosis, possibly in combination with GIP receptor agonism [46]. In vitro, GLP-2 in high concentrations can activate the GIP receptor [43]. However, in humans, when GLP-2 was co-administered with a GIP receptor antagonist, a preserved effect of GLP-2 on bone resorption was shown indicating a GLP-2 receptor-mediated effect [43]. In patients with hypoparathyroidism (due to thyroidectomy), the effect of exogenous GLP-2 is absent [44]. Further, GLP-2 receptors were low in osteoblasts, not detectable in osteoclasts but detected in parathyroid tissue [44]. Together, this may indicate that the effect of GLP-2 on bone is dependent of the parathyroid gland and/or parathyroid hormone. Interestingly, exogenous GLP-2 suppressed CTX-I in patients with ileostomy but not in patients with jejunostomy [62, 63]. Likewise, GLP-2 also suppressed parathyroid hormone in patients with ileostomy but not in patients with jejunostomy [62]. This suggests that the distal part of the small intestine may be of importance for the effects of GLP-2 on parathyroid hormone and secondarily bone resorption. As a hypothesis, GLP-2 may increase intestinal calcium uptake leading to decreasing parathyroid hormone [60].

Gut Hormones and Bone (Patho)physiology in Diabetes

The insulinotropic effect of GIP is severely impaired in patients with T2D [68, 69] but this does not seem to apply to the suppressive effect of GIP on bone resorption. Exogenous GIP infused in pharmacological doses during various levels of plasma glucose levels (from 3 to 12 mmol/l) in patients with T2D, reduced bone resorption (assessed by CTX-I) by ~30% compared to placebo [70•]. Also, GIP induced quite small, but statistically significant increases in bone formation (assessed by P1NP) [70•]. The effects of endogenous GIP on bone in patients with T2D have been investigated using the GIP receptor antagonist GIP(3-30)NH_2. Endogenous GIP contributed to about half of the postprandial suppression of bone resorption (assessed by CTX-I) in ten men with overweight and T2D [71•] supporting the notion that the effect of GIP on bone resorption in T2D is—at least partly—preserved. There were, however, considerable interindividual differences in this outcome, and patients with T2D and healthy controls have not been compared directly (i.e., in the same study) [71•].

Longer-term effects of GIP on bone turnover have, to our knowledge, so far, only been investigated in patients with T1D. After continuous subcutaneous infusion of GIP for 6 days [72], CTX-I was unchanged although a robust decline was observed in the first hours of the infusion [73]. This suggests that tachyphylaxis may develop after prolonged, continuous GIP administration/agonism, although this has yet to be confirmed.

In a clinical experiment [15], the effect of OGTT on CTX-I and P1NP was compared to separate and combined effects of GIP, GLP-1, and GLP-2 infused during IIGIs in patients with T2D. The infusions were designed to mimic the postprandial

plasma responses of the three gut hormones [74]. The combinatorial infusion of GIP, GLP-1, and GLP-2 during IIGI mimicked the suppression of CTX-I seen during an OGTT while the individual infusions had little or no effect on suppression of bone resorption compared to IIGI with concomitant saline infusion [15]. Unfortunately, no healthy control participants were included in these studies precluding conclusions on T2D-related bone pathophysiology. Nevertheless, the findings support that gut stimulation is of importance for postprandial suppression of bone resorption also in T2D. Additionally, the results allude to complicated and currently uncertain relationships between the effects of endogenous vs. exogenous gut hormones and 'postprandial' bone resorption.

As mentioned, the effect of gut hormonal infusions on circulating BTMs has been investigated in patients with T1D. The effects of intravenous infusions of GIP and GLP-1 both in pharmacological doses were investigated separately at plasma glucose concentrations between 3 to 7 mmol/l induced by insulin infusion. After 90 min, GIP induced a robust decline in CTX-I to ~41% of baseline levels, while GLP-1 induced a reduction similar to saline (placebo). When plasma glucose levels were clamped at 12 mmol/l, using an adjustable intravenous glucose infusion, the same results were found for GIP (and saline), while GLP-1 was not investigated in this setting [31••]. These results emphasize that the suppressive effect of GIP on bone resorption is independent of prevailing plasma glucose levels and unlikely to be mediated by GIP-induced insulin secretion. Secondly, the results also indirectly support that postprandial suppression of bone suppression is—at least partly—preserved in T1D as the suppressive effects on bone of GIP is not insulin-mediated.

In order to capture potential diabetic changes in diurnal bone resorption, Hygum et al. measured BTMs in patients with T1D and T2D, respectively, as well as in healthy controls over 24 h including standardized meals [9•]. Interestingly, the T2D group had slightly but statistically significantly lower P1NP levels compared to both patients with T1D and healthy controls with the latter comparison being in line with observations in bigger cohorts [75–77]. There were no differences between groups in diurnal variation of CTX-I, but these results should be interpreted cautiously due to the small sample size in the study ($N = 5$ in each group) and the variability of CTX-I measures. Despite the non-significant results, the methodological approach with repeated measures of CTX-I throughout the day is interesting in the light of the diurnal variation in bone resorption.

Effects of Incretin-Based Therapies on Bone in Diabetes

Incretin hormones are rapidly cleaved and, thus, inactivated by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4). Two drug classes utilize activation of incretin hormone receptors therapeutically: 1) DPP-4 inhibitors raising levels of the intact and active forms of endogenous incretin hormones for the treatment T2D, and 2) DPP-4 resistant GLP-1RAs for the treatment of obesity and T2D, respectively [17, 53]. Recently, tirzepatide, a dual GIP/GLP-1 receptor agonist, was approved for the treatment of T2D [78].

Incretin-based therapies in general have not been associated with safety issues regarding fractures. The effects of incretin-based therapies on fracture risk have to our knowledge not been investigated as a primary outcome in clinical trials but have been included in several meta-analyses. In a meta-analysis comprising 110 randomized clinical trials comparing incretin-based treatment modalities with placebo or active drugs for a minimum of 12 weeks in patients with T2D (total $N = 111{,}539$) and including data on bone fractures, Kong et al. found specific doses of the DPP-4 inhibitor sitagliptin (100 mg) and the GLP-1RA liraglutide (1.8 mg) to be associated with decreased fracture risk [79]. In another meta-analysis, comprising 38 randomized clinical trials comparing GLP-1RA treatment with placebo or other anti-diabetic drugs for a minimum of 24 weeks in patients with T2D (total $N = 39{,}795$) and including data on bone fractures, Cheng et al. found a protective effect of GLP-1RAs when follow-up was >52 weeks [80], a finding which seems driven by results from two studies of liraglutide and lixisenatide, respectively [81, 82]. In a network meta-analysis, Zhang et al. found that treatment with the GLP-1RA albiglutide was associated with decreased fracture risk [83]. In a meta-analysis of observational studies, a non-significant trend towards decreased fracture risk in users of DPP-4 inhibitors or GLP-1RAs was seen, and in a subgroup analysis, the use of GLP-1RAs was associated with a considerably decreased risk of hip fractures [84]. The above-mentioned meta-analytical findings suggesting a protective effect of GLP-1RA treatment in terms of fracture risk seem compatible with findings of increased hip BMD after GLP-1RA treatment [85, 86•]. Overall, GLP-1RAs and DPP-4 inhibitors for the treatment of T2D seem safe regarding fractures without clear favorable effects, nevertheless. These meta-analytical data need to be interpreted cautiously since fractures typically 1) do not represent adverse events of primary interest, 2) are not assessed in detail, and 3) comprise low-prevalent adverse events. Also, fracture site and severity may not have been accounted for; vertebral fractures may have been overlooked; and short treatment periods may cause hypoglycaemia-related fractures to weigh more than fragility fractures due to alterations of bone strength. Furthermore, the comparator is often other active compounds. Together, this complicates the interpretation of these meta-analytical results [87, 88].

In recent years, the effects of GLP-1RA on BMD and BTM have been reported from relatively short (24–52 weeks) and small ($n \leq 108$) randomized clinical trials including patients

with T1D and T2D, respectively (Table 1). In a randomized clinical trial investigating the effects of liraglutide on BTMs and BMD in patients with T2D, liraglutide maintained hip BMD after 26 weeks compared to placebo. Liraglutide had no effects on CTX-I, the primary outcome, while P1NP decreased after 1 and 4 weeks and then returned to baseline levels [86•]. In another study, patients with T2D were randomized to treatment with one of the two once-weekly GLP-1RAs long-acting exenatide and dulaglutide, respectively, insulin glargine or placebo. After 1 year, BMD was measured at lumbar vertebral bodies (L1-L4), the femoral neck, and the total hip. BMD decreased in the placebo group, was unchanged for insulin glargine and dulaglutide, and increased in the exenatide group [85]. Two studies investigated the use of GLP-1RAs vs. placebo in the management of T1D. Meal-time administrated short-acting exenatide did not have any effect on CTX-I, P1NP or BMD (hip, lumbar, and forearm) after 26 weeks compared to placebo [89]. Likewise, liraglutide showed no effect on CTX-I, P1NP or BMD (femoral neck) compared to placebo after 24 weeks [90].

Overall, GLP-1RAs do not change BMD in patients with T1D [89, 90] while hip BMD is increased or maintained compared to placebo in patients with T2D [85, 86]. No consistent changes are observed in BTM [86•, 89, 90]. However, GLP-1RA treatment is associated with weight loss, and in this context, the absence of a decline in BMD has been interpreted as an ability of the GLP-1RAs to preserve BMD during GLP-1RA-induced body weight loss compared to diet-induced weight loss which may decrease BMD [54, 91, 92]. Although BMD is typically normal or increased in T2D [4–6], BMD is still predictive of fracture risk in patients with T2D [93, 94]. Accordingly, other factors potentially contribute to bone fragility in diabetes (such as bone microstructure and advanced glycosylation end-products) and fractures (e.g., falls due to hypoglycaemia and neuropathy) [95].

A GLP-2 receptor agonist, teduglutide, is approved for treatment of short bowel syndrome [59], while another, glepaglutide, is under development [96]. However, to our knowledge, the effects of these drugs on bone outcomes are very limited although they, according to knowledge from native GLP-2, hold a potential to influence bone metabolism. In 16 patients with short-bowel syndrome, glepaglutide did not change bone mineral content after three weeks [96]. Thus, it is too early to draw conclusions on the effects of GLP-2-based therapies on bone health.

Future Perspectives

The human studies reviewed here give a clear picture of an endocrine gut-bone hormone axis but the role of this axis in diabetic bone fragility is uncertain. Investigations of genetic loss-of-function variants of the GIP receptor suggest that disturbance of GIP signalling impacts bone health [49, 50]. Except for this, potential disturbances of postprandial suppression of bone resorption have not been associated with bone

Table 1 Overview of recent randomized clinical trials reporting on effects of GLP-1RA therapy on bone mineral density and bone turnover markers in patients with diabetes

Study	Study design	Effect
Dejgaard et al. [90]	Population: T1D (N = 100) Intervention: Liraglutide 1.8 mg OD vs. placebo (add-on to existing insulin treatment) Duration: 24 weeks	No effect on BMD, P1NP or CTX-I despite significant weight loss (6.8 kg) in the liraglutide-treated group
Johansen et al. [89]	Population: T1D (N = 105) Intervention: Preprandial (3 times daily) 10 μg short-acting exenatide vs. placebo (add-on to existing insulin treatment) Duration: 26 weeks	No effect on BMD, P1NP or CTX-I despite significant weight loss (4.4 kg) in the exenatide-treated group
Cai et al. [85]	Population: T2D (N = 65) Intervention: Exenatide 2 mg OW (N = 19) vs. dulaglutide 1.5 mg OW (N = 19) vs. insulin glargine 6 IE/day (N = 10) vs. placebo OW (N = 17) Duration: 52 weeks	Exenatide and to a lesser extent dulaglutide were associated with increased BMD primarily at the hip compared to placebo (weight loss non-significant for exenatide and dulaglutide compared to placebo)
Hygum et al. [86•]	Population: T2D (N = 60) Intervention: Liraglutide 1.8 mg vs. placebo Duration: 26 weeks	Liraglutide decreased P1NP after one and four weeks without effects after 26 weeks. No effect on CTX-I. Hip BMD remained stable in the liraglutide-treated group compared to a decline in placebo-treated (liraglutide-induced weight-loss: 3.8 kg).

BMD, bone mineral density; *CTX-I*, C-terminal telopeptide of type I collagen; *P1NP*, N-terminal propeptide of type I procollagen; *GLP-1RA*, glucagon-like peptide 1 receptor agonist; *N*, number of participants; *OD*, once daily; *OW*, once weekly; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes

fragility. As bone resorption (assessed by CTX-I) varies diurnally, a fasting sample of CTX-I is an insufficient measure of bone resorption. Repeated sampling over 24 h in big cohorts is comprehensive but could potentially reveal associations to bone health (i.e., BMD, cortical porosity or other structural measures of bone tissue). Alternatively, large cohorts, where 2 h-OGTTs have been performed, could be used to investigate the postprandial suppression of bone resorption by analysing CTX-I [97]. This could reveal associations between postprandial changes in CTX-I and potential outcomes related to bone health (BMD or fracture risk) or exposures (e.g., states of diabetes, hepatic fat content and obesity).

GIP is a potent suppressor of bone resorption and the GIP receptor constitutes a potential target for treatment of bone fragility or osteoporosis, but the effects of GIP on bone metabolism have mostly been studied for shorter periods (up to 4 h). As mentioned, infusion of pharmacological GIP for 6 days in patients with T1D only intermittently lowered CTX-I [73] suggestive of tachyphylaxis. The dual GLP-1/GIP receptor agonist tirzepatide recently approved by the US Food and Drug Administration for treatment of T2D has shown promising results as treatment of obesity also [98, 99]. Effects of bone parameters have not been reported except for fractures reported as adverse events which were very few in number and have not raised concerns and labelled as a side effect.

Other gut hormones may also regulate bone metabolism. Recently, postprandial concentrations of the gut hormone peptide YY (PYY) have been associated with postprandial suppression of bone resorption [100] and knock-out of PYY in mice supports a role of PYY in regulation of bone metabolism [101]. Although effects of PYY infusions have been studied in humans [102], bone outcomes have, to our knowledge, not been reported.

As mentioned above, some of the suppressive effects of GLP-1 and GIP on bone resorption may be via insulin. Other pancreas hormones could also be involved. Amylin, a peptide co-secreted with insulin from the beta cell, has been associated with inhibitory effects on bone resorption in animal models [103], and in vitro, amylin increases proliferation of human osteoblasts [104]. The effects of amylin on bone metabolism in humans are unknown.

Conclusions

In recent years, knowledge on the link between the endocrine gut and bone physiology has expanded rapidly. Especially, the suppressive effects of the two gut hormones GIP and GLP-2 on postprandial suppression of bone resorption have been consolidated, while the role of GLP-1 remains uncertain. Most results are nevertheless from studies with small sample sizes and different interventions (OGTT, meals, infusions of native hormones in physiological and pharmacological doses), methods, and outcomes (timepoints, absolute and relative changes, AUCs etc.) making the studies and results challenging to compare. Disturbances of gut hormone actions are part of the pathophysiology of T2D but whether the endocrine gut-bone axis is disturbed in T2D is currently unknown. In patients with T1D, the suppressive effect of GIP on bone resorption is—at least partly—preserved, while GLP-1 seems without acute effects on bone metabolism. Therapies based on activation of incretin receptors (DPP-4 inhibitors, GLP-1RAs, and dual GIP/GLP-1 receptor agonists) seem to be overall safe regarding fracture risk although bone health has not been a primary focus of these studies, and no clinical studies have investigated the effect of incretin-based treatments on fracture risk as a primary outcome. The next generations of therapies based on GIP and/or GLP-2 receptor activation hold an interesting, but still hypothetical potential to affect bone health, both for patients with T1D and for patients with T2D, and possibly also for non-diabetic patients with osteoporosis. Ideally, this should be assessed in large-scale trials with fractures as the main outcome.

Author Contribution H.M. and M.H. searched and analyzed the relevant literature and drafted the manuscript. LSG prepared the figure. All authors wrote, edited, and approved the present manuscript.

Declarations

Conflict of Interest H.M. and M.M.H declare no conflict of interest. L.S.G. is minority shareholder of Antag Therapeutics. T.V. has served on scientific advisory panels, been part of speaker's bureaus for, served as a consultant to and/or received research support from Abbot, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, MSD/Merck, Novo Nordisk, Sanofi, and Sun Pharmaceuticals. F.K.K. has served on scientific advisory panels, been part of speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MedImmune, MSD/Merck, Norgine, Novo Nordisk, Sanofi, ShouTi, SNIPR Biome, Zealand Pharma and Zucara; and is a minority shareholder of Antag Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain original data from studies with human or animal subjects.

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