Journal of Clinical & Translational Endocrinology 40 (2025) 100392

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Effect of GIP and GLP-1 infusion on bone resorption in glucose intolerant, pancreatic insufficient cystic fibrosis

Wang Shin Lei [a], XianYan Chen [b], Lingyu Zhao [c], Tanicia Daley [d], Bradley Phillips [e], Michael R. Rickels [f], Andrea Kelly [g], Joseph M. Kindler [a,*]

[a] Department of Nutritional Sciences, The University of Georgia, Athens, GA, USA
[b] Department of Epidemiology & Biostatistics, The University of Georgia, Athens, GA, USA
[c] Department of Statistics, The University of Georgia, Athens, GA, USA
[d] Department of Pediatrics, Division of Endocrinology and Metabolism, Emory University School of Medicine, Atlanta, GA, USA
[e] College of Pharmacy and Biomedical & Translational Sciences Institute, The University of Georgia, Athens, GA, USA
[f] Department of Medicine, Division of Endocrinology, Diabetes & Metabolism, and Institute for Diabetes, Obesity & Metabolism, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[g] Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

ARTICLE INFO

Keywords:
Incretins
GLP-1
GIP
Bone Resorption
Cystic Fibrosis

ABSTRACT

Context: Diabetes and bone disease are common in cystic fibrosis (CF) and primarily occur alongside exocrine pancreatic insufficiency (PI). "Incretins," glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), augment insulin secretion and regulate bone metabolism. In CF, PI dampens the incretin response. Loss of the insulinotropic effect of GIP in CF was recently identified, but effects on bone are unknown.
Objective: Determine effects of incretins on bone resorption markers in adults with PI-CF.
Design: Secondary analysis of a mechanistic double-blinded randomized placebo-controlled crossover trial including adults ages 18–40 years with PI-CF (n = 25).
Intervention: Adults with PI-CF received either GIP (4 pmol/kg/min) or GLP-1 (1.5 pmol/kg/min) infusion, followed by double-blind randomization to either incretin or placebo infusion. Non-CF healthy controls received double-blind GIP (4 pmol/kg/min) or placebo. Serum C-terminal telopeptide (CTX), a bone resorption marker, was assessed during the infusion over 80 (GIP) or 60 (GLP-1) minutes.
Main Outcome Measures: CTX (mg/dL) concentrations.
Results: In PI-CF, CTX decreased during GIP infusion, but not during placebo (time-by-treatment interaction $P < 0.01$). GLP-1 did not affect CTX. In non-CF healthy controls, time-by-treatment interaction was not significant ($P = 0.23$), but CTX decreased during GIP ($P = 0.02$) but not placebo ($P = 0.47$).
Conclusions: GIP evokes a bone anti-resorptive effect in people with PI-CF. Since the incretin response is perturbed in PI-CF, and an infusion of GIP lowers bone resorption, the "gut-bone axis" in CF-related bone disease requires attention.

Introduction

Cystic fibrosis (CF) is a genetic disorder arising from recessive mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) [1]. Recurrent pulmonary infections and compromised lung function characterize CF, but non-pulmonary complications, including CF-related diabetes (CFRD) and CF-related bone disease (CFBD) are also common, particularly with increasing age [2]. According to the 2022 CF Foundation Registry [3], >40 % of adults have CFRD and > 30 % have CFBD. An extensive body of evidence links both type 1 diabetes and type 2 diabetes to bone health deficits and increased risk for fracture in non-CF populations [4–6], suggesting that CFRD might contribute to CFBD. Limited studies in people with CF have found that diabetes is associated with worse bone health [7,8], but biological

Abbreviations: CF, cystic fibrosis; PI, pancreatic insufficiency; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; CTX, C-terminal telopeptide of type 1 collagen.

* Corresponding author at: Department of Nutritional Sciences, The University of Georgia, Dawson Hall, Room 281, Athens, GA, USA 30602.
E-mail address: kindlerj@uga.edu (J.M. Kindler).

https://doi.org/10.1016/j.jcte.2025.100392
Received 7 September 2024; Received in revised form 22 March 2025; Accepted 4 April 2025
Available online 7 April 2025

mechanisms linking CFRD and CFBD have received limited attention.

The adult skeleton relies on a finely orchestrated interplay between osteoclast-mediated bone resorption and osteoblast-mediated bone formation for bone remodeling [9]. Disruptions in this process can lead to the development of osteoporosis, characterized by low bone density and vulnerability to fracture [10]. Many modifiable factors, including nutritional status and food intake, influence bone metabolism [11]. Following ingestion of a meal or isolated macronutrients, as in an oral glucose tolerance test (OGTT), a rapid and acute reduction in C-terminal telopeptide (CTX), a biomarker of bone resorption, occurs and signifies a decrease in bone resorption [12–15]. Providing potential mechanistic insights, the effects of glucose on bone resorption are more pronounced with enteral administration vs intravenous infusion or injection [15–17]. The dampened effect that occurs with bypassing of the gastrointestinal tract suggests that mechanisms mediated through the gut likely play a significant role in post-prandial bone metabolism.

In response to food ingestion, enteroendocrine K- and L-cells secrete glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), respectively [18]. These hormones are involved in regulating satiety, gastric motility, and insulin secretion to regulate glucose [19]. Both GIP and GLP-1 bind to specific G-protein coupled receptors to stimulate glucose-dependent pancreatic β-cell insulin secretion [20]. In addition to their well-established roles in insulin production for glucose control, incretins are also involved in regulating bone metabolism [21,22]. In clinical studies, short-term intravenous infusion of GIP reduces bone resorption in people with type 2 diabetes. GLP-1 receptors have been identified in primary mouse osteoblasts [23,24] and osteoclasts [23,24]. The impact of GLP-1 on human bone metabolism remains unclear. Insulin, a well-known anabolic hormone, also plays a role in bone turnover [25]. Accordingly, medical conditions like CF, characterized by disrupted incretin and insulin responses [26,27] and a diminished insulinotropic effect of GIP [28] may jeopardize bone health by altering the gut-bone axis.

The primary goal of this study was to determine the effect of incretins on a biomarker of bone resorption in adults with CF. Using data and blood specimens from a previously completed mechanistic double-blinded randomized placebo-controlled crossover study in adults with CF, we compared changes in CTX during GIP or GLP-1 infusion vs. placebo [28]. Based on prior research conducted in healthy adults [17,29–31], we hypothesized that GIP, but not GLP-1, infusion would result in a decrease in CTX compared to placebo.

Methods

Study design and participants

We performed a secondary analysis of data and blood specimens from a double-blinded randomized placebo-controlled crossover trial in adults with CF that was conducted at the Hospital of the University of Pennsylvania. The study design and participants are described in greater detail elsewhere [28]. Briefly, the goal of the original trial was to determine the effects of intravenous infusion of GIP and GLP-1 on pancreatic islet function in people with pancreatic insufficient CF (PI-CF). The current study includes 25 adults with PI-CF and 3 non-CF healthy controls that participated in the original trial and had sufficient stored blood specimens for the assessment of our primary outcome of interest. The availability of stored blood specimens restricted the sample size of the healthy control group.

To be eligible for inclusion into the original study, all subjects were required to be ≥ 18 years of age at the time of enrollment. Confirmation of CF diagnosis was established through *CFTR* mutation analysis and/or a positive sweat test. These diagnostic criteria adhered to the requirements set by the CF Foundation [32]. Exocrine PI was confirmed by the need for pancreatic enzyme replacement therapy. For individuals with PI-CF, subjects were required to have undergone a 75 g OGTT within six months of enrollment to determine their glucose tolerance status. All subjects were required to have abnormal glucose tolerance defined as follows: early glucose intolerance (1-hour glucose ≥ 155 mg/dL, 2-hour glucose < 140 mg/dL [33], impaired glucose tolerance (2-hour glucose 140–199 mg/dL), or CFRD without fasting hyperglycemia (2-hour glucose ≥ 200 mg/dL or previously confirmed CFRD diagnosis with fasting glucose < 126 mg/dL).

The randomization scheme is illustrated in Fig. 1. People with PI-CF were randomly assigned to either the GIP or GLP-1 infusion group. In addition to receiving the active incretin to which they were assigned (either GIP or GLP-1), participants underwent double-blind randomized administration of a placebo infusion on a different day. Healthy controls without CF were all assigned to receive GIP infusion. On a separate day, they also completed a double-blind randomized placebo infusion. The active and placebo experiments were performed in random order within 1–4 weeks of each other.

All study protocols and procedures were approved by the University of Pennsylvania and the Children's Hospital of Philadelphia Institutional Review Board for Human Subjects. The study was conducted under an Investigational New Drug application with the US Food and Drug Administration (IND 117381), and the protocol was registered with ClinicalTrials.gov (NCT01851694). Prior to beginning study procedures, all participants provided written informed consent.

Incretin administration

The experimental protocol has been reported previously [28]. The current study includes only measurements from the early-phase period of the experiment due to limited availability of stored blood specimens during the later time points. The experimental protocol is illustrated in Fig. 2.

Briefly, subjects underwent an infusion protocol, either involving incretin or placebo, on two separate days in a randomized and double-blinded cross-over fashion. Their visit to the clinical research center occurred in the morning following an overnight fast. The evening before each study visit, lyophilized GIP (1–42 amide) or GLP-1 (7–36 amide) was reconstituted in a solution consisting of 0.9 % saline and 0.25 % human serum albumin, resulting in a solution with a concentration of 1 ug/mL, or placebo was made as a solution consisting of 0.9 % saline and 0.25 % human serum albumin in order to mask appearance. Baseline fasting blood samples were collected at minutes −5 and 0 using an indwelling catheter inserted into a forearm vein. Following the minute 0 blood draw, the infusion of either incretin or saline commenced. Over the course of the infusion period from minutes 0 to 90, GIP was administered at a rate of 4 pmol/kg/min, whereas GLP-1 was administrated at a rate of 1.5 pmol/kg/min. The infusion rate for each incretin over the first 10 min of infusion was doubled to rapidly achieve steady-state concentrations. These rates and resulting concentrations of GIP and GLP-1 are considered supraphysiologic, and have been previously demonstrated to enhance insulin response in individuals with impaired glucose tolerance and type 2 diabetes [28,34,35].

Following the minute 30 specimen collection, 5 g of 10 % arginine was infused over a 1-minute period as part of the glucose-potentiated arginine (GPA) test. Subsequently, at minute 40, a hyperglycemic clamp was initiated using a variable-rate infusion of a 20 % glucose solution to achieve and maintain a plasma glucose concentration of approximately 230 mg/dL. In people with CF, those that were assigned to the GIP group had stored blood specimens available at minute 80, and those that were assigned to the GLP-1 group had stored blood specimens available at minute 60. In non-CF healthy controls, stored blood specimens were available at minute 60.

Blood biochemistries.

Blood samples were collected in EDTA tubes that had protease inhibitors, including dipeptidyl peptidase-4 inhibitor, added immediately following collection. Samples were then centrifuged at 4 °C, and plasma separated and frozen at −80 °C for future analyses. Total GIP and active GLP-1 were assayed and measured in duplicate by ELISA (Millipore,

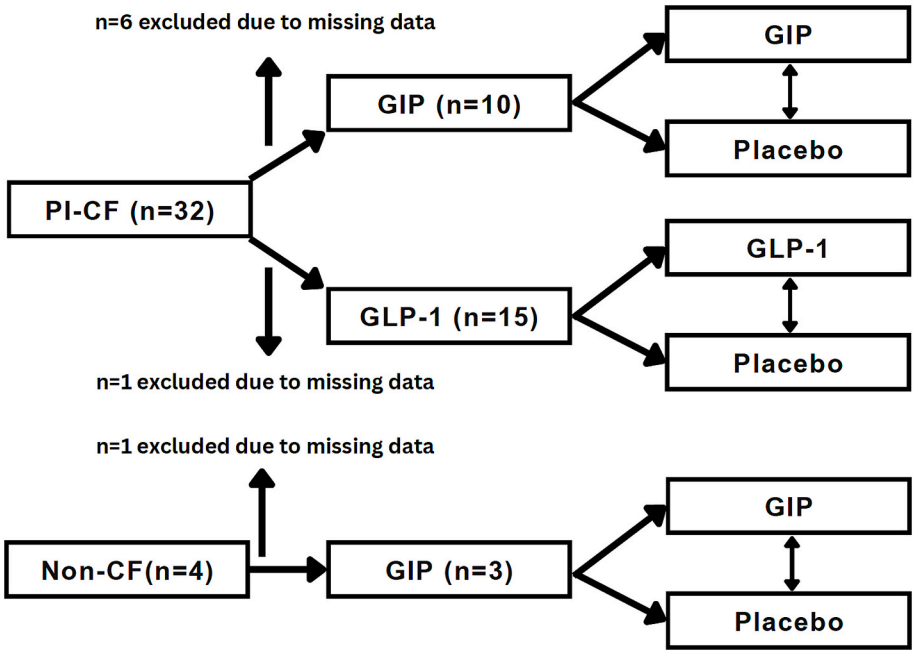

Fig. 1. Schematic depicting the crossover design and flow of participants throughout the study.

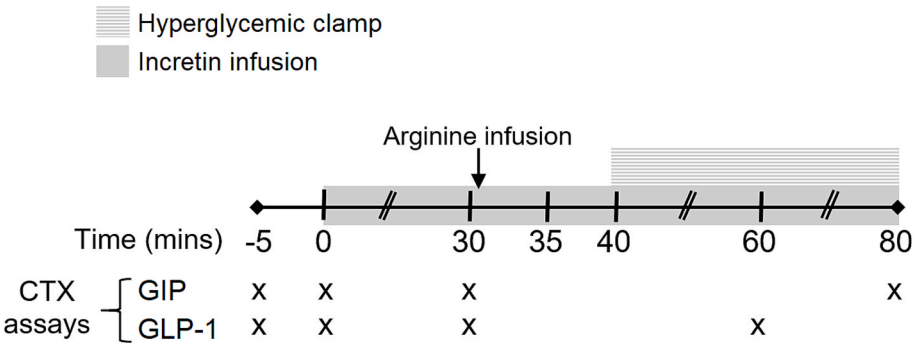

Fig. 2. Schematic depicting the experimental protocol.

Billerica, Massachusetts). CTX was evaluated using the Cobas e411 automated analyzer (Roche Diagnostics International ltd., Basel, Switzerland). Percent change relative to baseline from minutes −5 to 30 was computed and is abbreviated as CTX%$\Delta_{-5\text{-}30}$.

Anthropometry

Standing height and weight were assessed using a wall-mounted stadiometer and electronic scale, respectively. Body mass index (kg/m^2) was calculated.

Pulmonary function

Forced expiratory volume in one second, the gold standard for evaluating pulmonary disease in CF, was collected for all subjects from a recent clinic appointment.

Statistical analysis

Data were visually inspected for outliers, non-normal distributions, and influential data points before conducting statistical analyses. All statistical analyses were performed with R version 4.2.2. Descriptive characteristics were summarized using mean (standard deviation) for continuous variables and count (percentage) for categorical variables.

Linear mixed effects models were used to compare CTX during incretin and placebo infusion in the GIP and GLP-1 groups separately. The models treat time, condition (incretin or placebo), and their interaction term as fixed effects, and subject, condition nested under subject, and individual slopes in condition nested under subject, as random effects. Post-hoc analyses were performed to compare the changes in CTX over time within each condition, using the minute −5 timepoint as the reference. Dunnett's method was used to adjust the P-value for multiple comparisons. Additional post-hoc analyses with Bonferroni adjustment were conducted to compare the changes of CTX between incretin and saline condition. A two-sample *t*-test was performed to compare changes in CTX during GIP infusion, expressed as CTX%$\Delta_{-5\text{-}30}$, between the CF and non-CF healthy control groups. For all analyses, significance was defined as P-values < 0.05 (two-tailed).

Results

Descriptive characteristics

Descriptive statistics are presented in Table 1. Sixty percent of the study sample was female (n = 15). The average age was 27.1 years and the average BMI was 23.3 kg/m^2. Forty-eight percent of participants had early glucose intolerance (n = 12), 36 % had impaired glucose tolerance (n = 9), and 16 % had CFRD without fasting hyperglycemia (n = 4).

Table 1
Participant characteristics (PI-CF, n = 25).

	Mean ± SD
Age, years	27.1 ± 7.4
Female, n (%)	15 (60)
White, n (%)	25 (100)
Height, cm	166.7 ± 11.0
Weight, kg	64.9 ± 13.6
BMI, kg/m^2	23.3 ± 3.8
Fasting glucose, mg/dL[a]	90.9 ± 9.4
1-hour glucose, mg/dL	210.8 ± 28.7
2-hour glucose, mg/dL	144.2 ± 67.7
HbA1c[a]	5.6 ± 0.4
Fasting GIP, pg/mL[a]	56.4 ± 40.3
Fasting GLP-1, pmol/L[a]	3.8 ± 2.1
Fasting CTX, ng/mL[a]	0.67 ± 0.3
FEV1 (% Predicted)	85.7 ± 21.2

BMI, body mass index; HbA1c, hemoglobin A1c; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; CTX, C-terminal telopeptide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

[a] Fasting measure from minute −5 of infusion.

Changes in CTX during incretin infusion

The effects of GIP and GLP-1 infusion on CTX in adults with PI-CF are illustrated in Fig. 3. GIP infusion had a significant effect on CTX compared to the placebo infusion, as supported by a significant time by treatment interaction (P = 0.013). During GIP infusion, CTX at minute 30 (P = 0.0002) and 80 (P = 0.012) were significantly lower than minute −5. When comparing the two conditions, the change in CTX from minute −5 to 30 was significantly greater under the GIP vs. placebo condition (P = 0.005), and this difference remained but was not statistically significant from minute −5 to 80 (P = 0.13). No differences in CTX under the GLP-1 vs. placebo condition were found.

The effects of GIP infusion on CTX in the three non-CF healthy controls are illustrated in Supplemental Fig. S1. Briefly, the time by treatment interaction was not significant (P = 0.23). However, CTX decreased significantly during GIP infusion (P = 0.02) but not during placebo infusion (P = 0.47).

Comparisons of changes in CTX during GIP infusion between CF and non-CF healthy control groups are shown in Supplemental Fig. S2**.** No significant differences were found when comparing CTX%$\Delta_{-5\text{-}30}$ between the two groups (P = 0.68). By minute 30, CTX changed by a mean

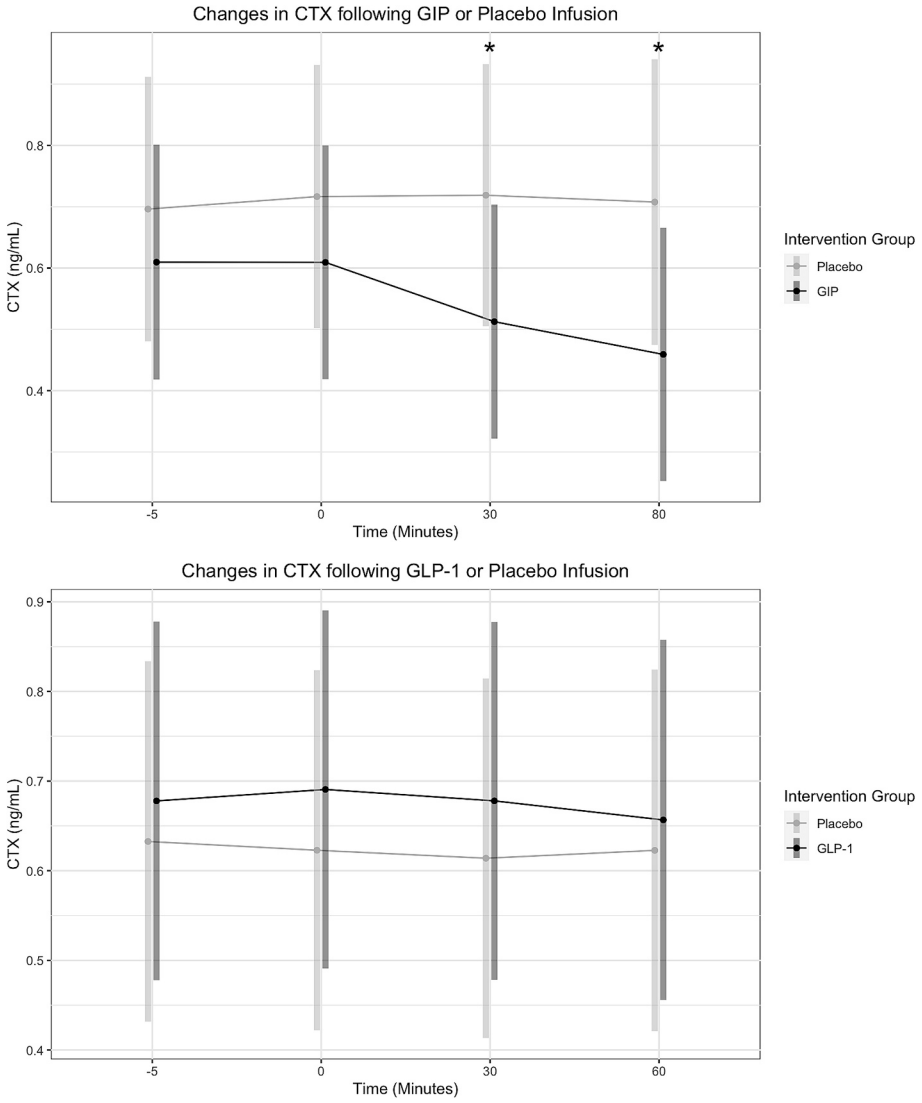

Fig. 3. CTX response to GIP (**A**) and GLP-1 (**B**) infusion in adults with PI-CF (n = 25). Data presented as means and vertical bands represent 95 % confidence interval. *Corresponding timepoint during GIP infusion differs significantly from minute −5 (P < 0.01). CTX, C-terminal telopeptide; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

of −14 ± 11 % and −17 ± 11 % in the CF and non-CF healthy controls, respectively.

Discussion

Incretins augment post-prandial insulin secretion to regulate glucose and also play a key role in bone metabolism [36]. Post-prandial incretin secretion and the insulinotropic effect of GIP are impaired in people with PI-CF [28,37], but the extent to which the bone anti-resorptive effect of GIP is preserved is unknown. This study experimentally tests the effect of incretin hormones on bone metabolism in adults with CF. Our main finding was that intravenous infusion of GIP yielded a significant decrease in bone resorption, as indicated by decreases in CTX, compared to placebo. Change in CTX during GIP infusion was similar between CF and non-CF healthy controls, but it is important to note that our small sample of non-CF healthy control subjects likely limited our statistical power to observe between-group differences. In contrast, GLP-1 did not affect CTX compared to placebo.

The primary aim of this study was to determine the effects of intravenous infusion of incretin hormones on bone resorption in adults with PI-CF. Pre-clinical studies indicate that osteoclasts possess receptors for GIP and that GIP treatment in osteoclast-osteoblast co-cultures inhibits osteoclast activity and delays bone resorption [38]. Clinical studies have further demonstrated that GIP administration via intravenous infusion or subcutaneous injection results in a significant decrease in CTX, a biomarker of bone resorption, thereby indicating a bone anti-resorptive effect [17,29,39–41]. Whereas the majority of these studies were conducted in otherwise healthy adults, few studies included people with type 1 diabetes [39], type 2 diabetes [40], and hypoparathyroidism [42]. In the current study of adults with PI-CF, we further report a significant decrease in CTX during intravenous GIP administration. This finding suggests that, despite the abnormal glucose tolerance status and impaired beta cell function observed in PI-CF, the marker of bone resorption in response to GIP remain intact. Nevertheless, the absence of an adequately sized non-CF healthy control group limits the interpretation of these findings.

The original trial from which blood specimens for the current study were derived included only a small number of non-CF healthy controls that underwent an identical GIP infusion protocol as the PI-CF group. While CTX was significantly reduced from minutes 0 to 30 in non-CF healthy controls during GIP infusion, the time by treatment interaction was not significant. Rather than GIP having a null biological effect on bone metabolism in people without CF, we suspect that our small sample size limited our power to detect significant differences between the GIP and placebo experiments, resulting in a potential false negative or type II error. Sufficiently powered studies that include an appropriate control group are required to determine whether the bone anti-resorptive effect of GIP is modified in people with CF.

In contrast to the findings relating to GIP, GLP-1 had a null effect on CTX. Osteoclasts possess membrane-bound GLP-1 receptors, and whole-body GLP-1-receptor knockout mice exhibit reduced bone mass and a significantly increased number of osteoclasts [24,43]. However, clinical studies have reported inconsistent effects of GLP-1 infusion or injection on biomarkers of bone resorption in humans [17,44]. In a rodent model of streptozotocin-induced type 1 diabetes, GLP-1 receptor agonism inhibited osteoclastogenesis by modifying the RANKL to OPG ratio [45]. A prior study from our lab involving healthy young adults found a positive association between GLP-1 and RANKL following a 75 g OGTT [13]. CF is associated with high bone turnover [46], and a greater RANKL/OPG ratio has been identified in people with CFBD compared to those without CFBD [47]. While we did not find significant associations between GLP-1 and CTX, previous clinical studies indicate that GLP-1 receptor agonists may influence biomarkers of bone turnover and bone density in people with type 2 diabetes [48,49], which highlights the need for studies investigating biological mechanisms linking GLP-1 to bone health.

Incretins play a key role in regulating insulin production for glucose control following a meal [50]. Beyond its known glucoregulatory effects, insulin is also suspected to impact bone metabolism by having a bone-augmenting effect [51,52]. Insulin deficiency, as in type 1 diabetes, is associated with bone deficits and increased risk for fracture [53,54]. While studies that have experimentally tested the effects of insulin on bone resorption are limited, recent studies in people with type 1 diabetes lacking endogenous insulin production have reported that insulin infusion did not significantly alter CTX [55], but GIP infusion led to a substantial decrease in CTX [39]. Similarly, a recent study in individuals with type 1 diabetes found that an OGTT and a subsequent isoglycemic intravenous glucose infusion significantly reduced CTX independent of plasma glucose excursion and insulin secretion [56]. In the present study that previously reported on the loss of GIP's insulinotropic action in PI-CF, the effect of GIP to suppress CTX in PI-CF occurred in the presence of similar concentrations of insulin that were not different under conditions of GIP or placebo infusion [28]. Results from these studies suggest that the effect of incretins on bone resorption may be independent of insulin

As with other studies [17,29,39–41], we used supraphysiological doses of GIP and GLP-1 for our experimental protocol. Although this approach might limit the direct translation of our results to the clinical settings, our findings support the potential for emerging incretin-based therapies, which have gained attention for treating obesity and type 2 diabetes [57], to impact bone health in patient populations that are vulnerable to musculoskeletal complications. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) and dual GIP/GLP-1 receptor agonists (e.g., tirzepatide) have demonstrated promising effects on weight loss and glycemic control in patients with and without diabetes [58–61]. Emerging evidence suggests that some of these incretin mimetic therapies influence bone metabolism by reducing bone resorption and promoting bone formation [49,62]. Although there has been conflicting evidence relating to fracture [63], in a 52-week clinical trial, the GLP-1 receptor agonist exenatide increased bone mineral density in patients with type 2 diabetes despite significant weight loss [48]. Given that weight loss is typically accompanied by bone demineralization [64], clinical studies examining incretin-based medications and fracture are needed.

Strengths and limitations of this study that should be taken into consideration when interpreting our results. We used previously acquired data and blood specimens from a double-blinded randomized placebo-controlled crossover trial that was aimed at investigating the β-cell response to GIP and GLP-1 infusion in adults with PI-CF. Leveraging existing data and blood specimens to investigate the causal link between incretins and bone metabolism in people with CF is a resourceful approach. Although the crossover design helps minimize potential confounding across subjects because each individual served as their own control, some subjects from the original study were not included in the current analyses due to insufficiently stored specimens for CTX assays. Thus, our statistical power to observe significant associations was limited. As described in greater detail in the parent study by Nyirjesy et al [28], the entire experimental protocol was about 260 min in duration. In addition to infusing GIP/GLP-1 or placebo, there were also components of the protocol that included arginine infusion for GPA stimulation testing during hyperglycemic clamping. Due to our small sample size, limited number of blood specimens, and potential confounding of glycemic status, we focused solely on the immediate period following incretin infusion. Arginine infusion was initiated after the minute 30 timepoint, so the initial decrease in CTX during the first 30 min of GIP infusion suggests that the reported effect of GIP on bone resorption is not confounded by arginine. Additionally, since the hyperglycemic clamp was initiated after the minute 40 timepoint, we performed analyses using data from minutes −5 to 30. CTX%$\Delta_{-5\text{-}30}$ did not differ significantly between the PI-CF and non-CF healthy controls. This suggests that these null findings were not confounded by hyperglycemia. Our study's observation period is shorter than other

investigations that extend up to 240 min following infusion [17], and limits our ability to capture long-term antiresorptive effects of incretin hormones. The lack of additional bone biomarkers, such as procollagen 1 intact N-terminal propeptide (P1NP), osteocalcin, RANKL, and OPG, due to limited sample availability, underscores the need for further investigation. RANKL and OPG regulate osteoblast differentiation and activation and are likely involved in incretin regulation of bone [65]. Additionally, GIP and GLP-1 have also been shown to upregulate bone formation by inhibiting osteocalcin synthesis in in-vitro models [66]. As such, assessing other biomarkers of bone turnover beyond CTX would provide important additional insight into mechanisms concerning the gut-bone axis in CF.

Conclusions

In conclusion, the results from this study suggest that GIP has a bone anti-resorptive effect in people with PI-CF. Maldigestion resulting from exocrine PI hinders the post-prandial GIP and GLP-1 response in people with CF [28], and the insulinotropic effect of GIP is suppressed in CF [28]. Since diabetes and bone disease are among the most common complications of CF, entero-endocrinopathies warrant further investigation with respect to their impact on skeletal health. With the emergence of incretin-based therapies for the treatment of type 2 diabetes and chronic weight management [67], combined with concerns regarding their effects on musculoskeletal outcomes, bone density and fracture should be studied in future clinical trials.

Disclosures: The authors have no disclosures.

Grants: This work was supported by the UGA Obesity Research Initiative (W.S.L.), Cystic Fibrosis Foundation grants LEI23H0 (W.S.L.) and RICKEL19A0-1 (M.R.R.; A.K.), Public Health Service Research grants KL2 TR002381 (J.M.K.), UL1 TR002378 (Georgia Clinical and Translational Science Alliance), R01 DK97830 (A.K.; M.R.R.), UL1 TR001878 (University of Pennsylvania Center for Human Phenomic Science), and P30 DK19525 (University of Pennsylvania Diabetes Research Center Radioimmunoassay & Biomarkers Core).

CRediT authorship contribution statement

Wang Shin Lei: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **XianYan Chen:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **Lingyu Zhao:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **Tanicia Daley:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Bradley Phillips:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Michael R. Rickels:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Andrea Kelly:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Joseph M. Kindler:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2025.100392.

References

[1] Tsui LC. "The cystic fibrosis transmembrane conductance regulator gene. *Am J Respir Crit Care Med* 1995;151(3 Pt 2):S47–53. https://doi.org/10.1164/ajrccm/151.3_Pt_2.S47.
[2] Sergeev V, Chou FY, Lam GY, Hamilton CM, Wilcox PG, Quon BS. "The extrapulmonary effects of cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. *Ann Am Thorac Soc* 2020;17(2):147–54. https://doi.org/10.1513/AnnalsATS.201909-671CME.
[3] Foundation CF. Cystic Fibrosis Foundation Patient Registry," in "2022 Annual Data Report. Maryland: Bethesda; 2022.
[4] Starup-Linde J, Hygum K, Harsløf T, Langdahl B. "Type 1 diabetes and bone fragility: links and risks. *Diabetes Metab Syndr Obes* 2019;12:2539–47. https://doi.org/10.2147/DMSO.S191091.
[5] Romero-Díaz C, Duarte-Montero D, Gutiérrez-Romero SA, Mendivil CO. "Diabetes and bone fragility. *Diabetes Ther* 2021;12(1):71–86. https://doi.org/10.1007/s13300-020-00964-1.
[6] Dhaliwal R, et al. "Determinants of fracture in adults with type 1 diabetes in the USA: Results from the T1D exchange clinic registry. *J Diabetes Complications* 2018;32(11):1006–11. https://doi.org/10.1016/j.jdiacomp.2018.08.016.
[7] Rana M, Munns CF, Selvadurai H, Briody J, Craig ME. "The impact of dysglycaemia on bone mineral accrual in young people with cystic fibrosis. *Clin Endocrinol* 2013;78(1):36–42. https://doi.org/10.1111/j.1365-2265.2012.04484.x.
[8] Mathiesen IH, et al. Markers of bone turnover are reduced in patients with CF related diabetes; the role of glucose. *J Cyst Fibros* 2019;18(3):436–41. https://doi.org/10.1016/j.jcf.2019.01.004.
[9] Kim J-M, Lin C, Stavre Z, Greenblatt MB, Shim J-H. "Osteoblast-osteoclast communication and bone homeostasis. *Cells* 2020;9(9):2073. https://doi.org/10.3390/cells9092073.
[10] Föger-Samwald U, Dovjak P, Azizi-Semrad U, Kerschan-Schindl K, Pietschmann P. "Osteoporosis: pathophysiology and therapeutic options. *EXCLI J* 2020;19:1017–37. https://doi.org/10.17179/excli2020-2591.
[11] S. L. Wilson-Barnes, S. A. Lanham-New, and H. Lambert, "Modifiable risk factors for bone health & fragility fractures," *Best Practice & Research Clinical Rheumatology*, p. 101758, 2022, DOI: 10.1016/j.berh.2022.101758.
[12] Lei WS, et al. Bone metabolism and incretin hormones following glucose ingestion in young adults with pancreatic insufficient cystic fibrosis. *J Clin Transl Endocrinol* 2022;30:100304. https://doi.org/10.1016/j.jcte.2022.100304.
[13] Lei WS, Rodrick EB, Belcher SL, Kelly A, Kindler JM. "Bone resorption and incretin hormones following glucose ingestion in healthy emerging adults. *J Clin Transl Endocrinol* 2023;31:100314. https://doi.org/10.1016/j.jcte.2023.100314.
[14] Maagensen H, Junker AE, Jørgensen NR, Gluud LL, Knop FK, Vilsbøll T. Bone turnover markers in patients with nonalcoholic fatty liver disease and/or type 2 diabetes during oral glucose and isoglycemic intravenous glucose. *J Clin Endocrinol Metab* 2018;103(5):2042–9. https://doi.org/10.1210/jc.2018-00176.
[15] Westberg-Rasmussen S, et al. Differential impact of glucose administered intravenously or orally on bone turnover markers in healthy male subjects. *Bone* 2017;97:261–6. https://doi.org/10.1016/j.bone.2017.01.027.
[16] Henriksen DB, et al. "Role of gastrointestinal hormones in postprandial reduction of bone resorption. *J Bone Miner Res* 2003;18(12):2180–9. https://doi.org/10.1359/jbmr.2003.18.12.2180.
[17] Bergmann NC, et al. Separate and combined Effects of GIP and GLP-1 infusions on bone metabolism in overweight men without diabetes. *J Clin Endocrinol Metab* 2019;104(7):2953–60. https://doi.org/10.1210/jc.2019-00008.
[18] Theodorakis MJ, et al. "Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Phys Endocrinol Metab* 2006;290(3):E550–9. https://doi.org/10.1152/ajpendo.00326.2004.
[19] T. Edholm *et al.*, "Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis," (in eng), *Neurogastroenterol Motil,* vol. 22, no. 11, pp. 1191-200, e315, 2010, doi: 10.1111/j.1365-2982.2010.01554.x.
[20] Seino Y, Fukushima M, Yabe D. "GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig* 2010;1(1–2):8–23. https://doi.org/10.1111/j.2040-1124.2010.00022.x.
[21] Dicembrini I, Mannucci E, Rotella CM. "Bone: incretin hormones perceiver or receiver? *Exp Diabetes Res* 2012;2012:519784. https://doi.org/10.1155/2012/519784.
[22] Yavropoulou MP, Yovos JG. Incretins and bone: Evolving concepts in nutrient-dependent regulation of bone turnover. *Hormones* 2013;12(2):214–23. https://doi.org/10.14310/horm.2002.1405.
[23] Mabilleau G, Pereira M, Chenu C. "Novel skeletal effects of glucagon-like peptide-1 (GLP-1) receptor agonists. *J Endocrinol* 2018;236(1):R29–42. https://doi.org/10.1530/joe-17-0278.
[24] Li Z, Li S, Wang N, Xue P, Li Y. Liraglutide, a glucagon-like peptide-1 receptor agonist, suppresses osteoclastogenesis through the inhibition of NF-κB and MAPK pathways via GLP-1R. *Biomed Pharmacother* 2020;130:110523. https://doi.org/10.1016/j.biopha.2020.110523.
[25] Cipriani C, et al. "The interplay between bone and glucose metabolism. Front Endocrinol 2020;11. https://doi.org/10.3389/fendo.2020.00122.
[26] Sun X, et al. "Incretin dysfunction and hyperglycemia in cystic fibrosis: Role of acyl-ghrelin. *J Cyst Fibros* 2019;18(4):557–65. https://doi.org/10.1016/j.jcf.2019.01.010.
[27] Kelly A, et al. "Islet hormone and incretin secretion in cystic fibrosis after four months of ivacaftor therapy. *Am J Respir Crit Care Med* 2019;199(3):342–51. https://doi.org/10.1164/rccm.201806-1018OC.

[28] Nyirjesy SC, et al. "Effects of GLP-1 and GIP on Islet function in glucose-intolerant, pancreatic-insufficient cystic fibrosis. *Diabetes* 2022;71(10):2153–65. https://doi.org/10.2337/db22-0399.
[29] Gasbjerg LS, et al. "GIP's effect on bone metabolism is reduced by the selective GIP receptor antagonist GIP(3-30)NH(2). *Bone* 2020;130:115079. https://doi.org/10.1016/j.bone.2019.115079.
[30] Nissen A, et al. A pilot study showing acute inhibitory effect of GLP-1 on the bone resorption marker CTX in humans. *JBMR Plus* 2019;3(10):e10209. https://doi.org/10.1002/jbm4.10209.
[31] Skov-Jeppesen K, Veedfald S, Madsbad S, Holst JJ, Rosenkilde MM, Hartmann B. "Subcutaneous GIP and GLP-2 inhibit nightly bone resorption in postmenopausal women: A preliminary study. *Bone* 2021;152:116065. https://doi.org/10.1016/j.bone.2021.116065.
[32] Farrell PM, et al. "Diagnosis of Cystic Fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr* 2017;181s:S4–15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064.
[33] Nyirjesy SC, et al. "β-Cell secretory defects are present in pancreatic insufficient cystic fibrosis with 1-hour oral glucose tolerance test glucose ≥155 mg/dL. *Pediatr Diabetes* 2018;19(7):1173–82. https://doi.org/10.1111/pedi.12700.
[34] Kjems LL, Holst JJ, Vølund A, Madsbad S. "The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects. *Diabetes* 2003;52(2):380–6. https://doi.org/10.2337/diabetes.52.2.380.
[35] Wice BM, et al. "Xenin-25 amplifies GIP-mediated insulin secretion in humans with normal and impaired glucose tolerance but not type 2 diabetes. *Diabetes* 2012;61(7):1793–800. https://doi.org/10.2337/db11-1451.
[36] Nauck M. "Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab* 2016;18(3):203–16. https://doi.org/10.1111/dom.12591.
[37] Kelly A, et al. "Effect of sitagliptin on islet function in pancreatic insufficient cystic fibrosis with abnormal glucose tolerance. *J Clin Endocrinol Metab* 2021;106(9):2617–34. https://doi.org/10.1210/clinem/dgab365.
[38] Hansen MS, et al. GIP reduces osteoclast activity and improves osteoblast survival in primary human bone cells. *Eur J Endocrinol* 2023;188(1):lvac004. https://doi.org/10.1093/ejendo/lvac004.
[39] Christensen MB, et al. Glucose-dependent insulinotropic polypeptide (GIP) inhibits bone resorption independently of insulin and glycemia. *J Clin Endocrinol Metab* 2018;103(1):288–94. https://doi.org/10.1210/jc.2017-01949.
[40] Christensen MB, Lund AB, Jørgensen NR, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide (GIP) reduces bone resorption in patients with type 2 diabetes. *J Endocr Soc* 2020;4(9):bvaa097. https://doi.org/10.1210/jendso/bvaa097.
[41] Nissen A, Christensen M, Knop FK, Vilsbøll T, Holst JJ, Hartmann B. Glucose-dependent insulinotropic polypeptide inhibits bone resorption in humans. *J Clin Endocrinol Metab* 2014;99(11):E2325–9. https://doi.org/10.1210/jc.2014-2547.
[42] Skov-Jeppesen K, et al. "The Antiresorptive Effect of GIP, But Not GLP-2, Is Preserved in Patients With Hypoparathyroidism-A Randomized Crossover Study. *J Bone Miner Res* 2021;36(8):1448–58. https://doi.org/10.1002/jbmr.4308.
[43] Yamada C, et al. "The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. *Endocrinology* 2008;149(2):574–9. https://doi.org/10.1210/en.2007-1292.
[44] Helsted MM, et al. The role of endogenous GIP and GLP-1 in postprandial bone homeostasis. *Bone* 2020;140:115553. https://doi.org/10.1016/j.bone.2020.115553.
[45] Yu J, et al. "Liraglutide inhibits osteoclastogenesis and improves bone loss by downregulating trem2 in female Type 1 diabetic mice: Findings from transcriptomics. Front Endocrinol 2021;12. https://doi.org/10.3389/fendo.2021.763646.
[46] Stalvey MS, Clines GA. "Cystic fibrosis-related bone disease: insights into a growing problem. *Curr Opin Endocrinol Diabetes Obes* 2013;20(6):547–52. https://doi.org/10.1097/01.med.0000436191.87727.ec.
[47] Abid S, et al. "Evaluation of an association between RANKL and OPG with bone disease in people with cystic fibrosis. *J Cyst Fibros* 2023;22(1):140–5. https://doi.org/10.1016/j.jcf.2022.08.011.
[48] Cai TT, et al. "Effects of GLP-1 receptor agonists on bone mineral density in patients with type 2 diabetes mellitus: A 52-week clinical study. *Biomed Res Int* 2021;2021:3361309. https://doi.org/10.1155/2021/3361309.
[49] Xie B, et al. The impact of glucagon-like peptide 1 receptor agonists on bone metabolism and its possible mechanisms in osteoporosis treatment. *Front Pharmacol* 2021;12:697442. https://doi.org/10.3389/fphar.2021.697442.
[50] Kim W, Egan JM. "The role of incretins in glucose homeostasis and diabetes treatment. *Pharmacol Rev* 2008;60(4):470–512. https://doi.org/10.1124/pr.108.000604.
[51] Thrailkill KM, Lumpkin Jr CK, Bunn RC, Kemp SF, Fowlkes JL. "Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. *Am J Phys Endocrinol Metab* 2005;289(5):E735–45. https://doi.org/10.1152/ajpendo.00159.2005.
[52] Klein GL. "Insulin and bone: Recent developments. *World J Diabetes* 2014;5(1):14–6. https://doi.org/10.4239/wjd.v5.i1.14.
[53] Sinha Gregory N, et al. "Diabetes risk factors and bone microarchitecture as assessed by high-resolution peripheral quantitative computed tomography in adults with long-standing type 1 diabetes. *Diabetes Care* 2023. https://doi.org/10.2337/dc23-0839.
[54] Emanuelsson F, Afzal S, Jørgensen NR, Nordestgaard BG, Benn M. "Hyperglycaemia, diabetes and risk of fragility fractures: observational and Mendelian randomisation studies. *Diabetologia* 2023. https://doi.org/10.1007/s00125-023-06054-8.
[55] Sherk VD, et al. "Acute hyperinsulinemia alters bone turnover in women and men with type 1 diabetes. *JBMR Plus* 2020;4(9):e10389. https://doi.org/10.1002/jbm4.10389.
[56] Hartmann B, et al. Signs of a glucose- and insulin-independent gut-bone axis and aberrant bone homeostasis in type 1 diabetes. *J Clin Endocrinol Metab* 2024;109(1):e259–65. https://doi.org/10.1210/clinem/dgad431.
[57] Q. Tan *et al.*, "Recent Advances in Incretin-Based Pharmacotherapies for the Treatment of Obesity and Diabetes," (in eng), *Front Endocrinol (Lausanne),* vol. 13, p. 838410, 2022, doi: 10.3389/fendo.2022.838410.
[58] J. Y. Wang *et al.*, "GLP-1 receptor agonists for the treatment of obesity: Role as a promising approach," (in eng), *Front Endocrinol (Lausanne),* vol. 14, p. 1085799, 2023, doi: 10.3389/fendo.2023.1085799.
[59] Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. *Cardiovasc Diabetol* 2022;21(1):169. https://doi.org/10.1186/s12933-022-01604-7.
[60] Okamoto A, Yokokawa H, Nagamine T, Fukuda H, Hisaoka T, Naito T. "Efficacy and safety of semaglutide in glycemic control, body weight management, lipid profiles and other biomarkers among obese type 2 diabetes patients initiated or switched to semaglutide from other GLP-1 receptor agonists. *J Diabetes Metab Disord* 2021;20(2):2121–8. https://doi.org/10.1007/s40200-021-00899-9.
[61] Wilding JPH, et al. "Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384(11):989–1002. https://doi.org/10.1056/NEJMoa2032183.
[62] Stensen S, Gasbjerg LS, Helsted MM, Hartmann B, Christensen MB, Knop FK. GIP and the gut-bone axis – physiological, pathophysiological and potential therapeutic implications. *Peptides* 2020;125:170197. https://doi.org/10.1016/j.peptides.2019.170197.
[63] H. Kitaura *et al.*, "Effects of Incretin-Related Diabetes Drugs on Bone Formation and Bone Resorption," (in eng), *Int J Mol Sci,* vol. 22, no. 12, 2021, doi: 10.3390/ijms22126578.
[64] Amariti J, et al. "Older women who are overweight or obese have vertebral abnormalities, partially degraded TBS, and BMD that worsen with weight loss. *Calcif Tissue Int* 2022;111(2):137–44. https://doi.org/10.1007/s00223-022-00973-1.
[65] Viggers R, Rasmussen N-H-H, Vestergaard P. Effects of incretin therapy on skeletal health in type 2 diabetes—A systematic review. *JBMR Plus* 2023;7(11):e10817. https://doi.org/10.1002/jbm4.10817.
[66] Kainuma S, et al. "Attenuation by incretins of thyroid hormone-stimulated osteocalcin synthesis in osteoblasts. *Biomed Rep* 2016;5(6):771–5. https://doi.org/10.3892/br.2016.798.
[67] Renner S, Blutke A, Streckel E, Wanke R, Wolf E. "Incretin actions and consequences of incretin-based therapies: lessons from complementary animal models. *J Pathol* 2016;238(2):345–58. https://doi.org/10.1002/path.4655.