Circulating Molecular Drivers of Bone Remodeling in Pancreatitis

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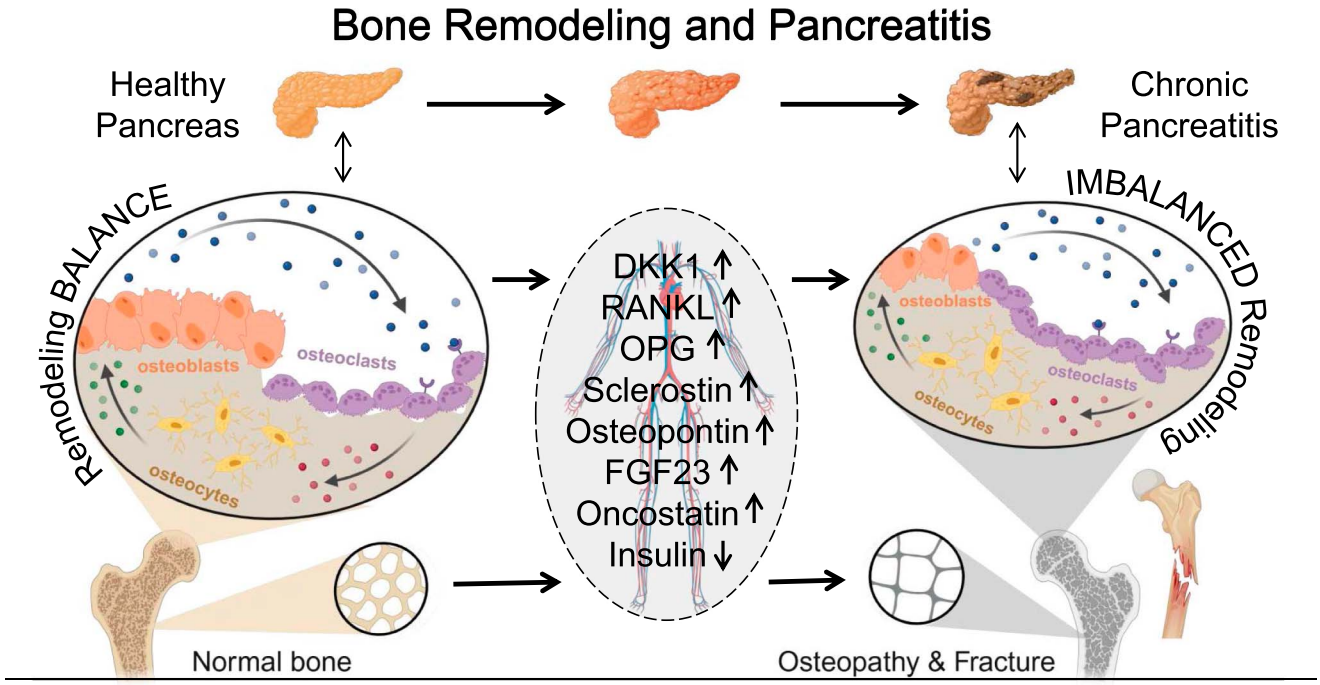
INTRODUCTION: **Pancreatitis-associated osteopathy is a clinically significant but mechanistically underexplored complication of pancreatic disease. We aimed to characterize stage-specific alterations in bone remodeling biomarkers across the spectrum of disease: recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP).**

METHODS: **In a cross-sectional analysis of North American Pancreatitis Study 2 participants, we measured serum mechanistic (sclerostin, dickkopf-1, receptor activator of nuclear factor κβ ligand, and osteoprotegerin), hormonal (fibroblast growth factor 23, insulin, and leptin), and modulatory (osteopontin, oncostatin, and osteoactivin) markers in controls (n = 30), RAP (n = 40), and CP (n = 40) using a multiplex assay. Group differences were assessed with ANOVA, Fisher exact test, and Kruskal-Wallis; multivariable regression identified predictors of biomarker variation.**



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RESULTS: **Eight of 10 biomarkers differed significantly among groups. Sclerostin, dickkopf-1, receptor activator of nuclear factor κβ ligand, and osteoprotegerin were elevated in RAP and CP vs controls, with the highest values in CP. The RANKL/OPG ratio was greatest in CP. Fibroblast growth factor 23 was increased in RAP, while insulin was reduced in CP. Osteopontin and oncostatin were elevated in pancreatitis groups, with osteopontin increasing progressively from control to RAP to CP. Several bone biomarker patterns varied by sex, tobacco, and alcohol use. Stepwise regression identified several significant predictors.**

DISCUSSION: **These findings represent the most comprehensive bone metabolism biomarker profiling in pancreatitis to date, revealing stage-specific dysregulation of bone remodeling. Findings suggest a shift toward increased bone resorption and impaired formation with disease progression. Larger longitudinal studies are needed for marker validation, to clarify mechanisms, and guide targeted interventions to reduce bone loss and fracture risk in this high-risk population.**

KEYWORDS: chronic pancreatitis; recurrent acute pancreatitis; bone remodeling; biomarkers; osteopathy

ABBREVIATIONS: ANOVA, analysis of variance; AP, acute pancreatitis; BMD, bone mineral density; BMI, body mass index; CP, chronic pancreatitis; CT, computed tomography; DKK1, dickkopf-1; FGF23, fibroblast growth factor 23; GI, gastrointestinal; MBD, metabolic bone disease; MRI, magnetic resonance imaging; NAPS2, North American Pancreatitis Study 2; NS, not significant; OPG, osteoprotegerin; PROCEED, PROspective Evaluation of Chronic Pancreatitis for EpidEmiologic and Translational StuDies; RANKL, receptor activator of nuclear factor κ (kappa) – β (beta) ligand; RAP, recurrent acute pancreatitis; SE, standard error

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B396, http://links.lww.com/CTG/B397, http://links.lww.com/CTG/B398, http://links.lww.com/CTG/B399, http://links.lww.com/CTG/B400

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INTRODUCTION

Pancreatitis is an inflammatory disease with acute and chronic manifestations, characterized by progressive anatomical, metabolic, and functional changes. The natural history of pancreatitis is variable; most patients present initially with acute pancreatitis (AP) or recurrent acute pancreatitis (RAP), with a subset progressing to chronic pancreatitis (CP) (1–4). Like other high-risk gastrointestinal disorders, patients with CP exhibit abnormal bone turnover (5,6) and reduced bone mineral density (BMD) indicating a decline in bone health. Previous studies, including an analysis of North American Pancreatitis Study 2 (NAPS2) participants, report elevated osteopathy rates and an increased fragility fracture risk in CP compared with controls (7–19).

Bone health is critical for maintaining skeletal integrity, muscle function, and fracture prevention. Clinically, serum levels of procollagen 1 amino-terminal propeptide and carboxy-terminal telopeptide of type I collagen are routinely used as markers for bone resorption and formation, respectively (20). Balanced levels of these and other factors including osteocalcin, parathyroid hormone, and bone alkaline phosphatase indicate bone health. Bone remodeling is governed by a complex interplay of signaling factors regulating bone turnover and mineralization. Disruptions in bone regulatory mechanisms in chronic inflammatory disorders contribute to metabolic bone disease (MBD, e.g., osteoporosis). Although other gastrointestinal diseases with metabolic complications alter bone turnover (21–25), pancreatitis uniquely involves both endocrine and exocrine dysfunction, potentially dysregulating key bone metabolism and remodeling pathways. Alterations linked to systemic inflammation, vitamin D deficiency, and an elevated fragility fracture risk in patients with pancreatitis (5,7,12–17,26) are attributed to prolonged inflammation, nutrient malabsorption and malnutrition (13), habitual smoking, alcohol use disorder, diabetes, female sex, advanced age, and reduced physical activity due to either disease burden or lifestyle changes (5,11,27,28). Although the relative contribution of these factors remains undetermined, a definitive link between pancreatitis and osteopathy exists, highlighting the need for a more comprehensive understanding of the metabolic and molecular mechanisms underlying bone loss in this population. Despite clinical evidence of BMD loss and altered bone turnover markers in CP, the underlying molecular mechanisms—and how they differ across stages of pancreatic disease (e.g., RAP vs CP)—remain poorly understood. It is unclear when these changes in bone health emerge or what drives the transition, highlighting a critical gap in our understanding of pancreatitis-associated osteopathy. Building on the

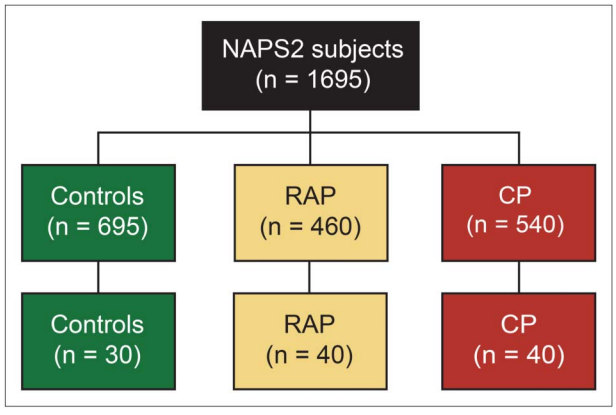

Figure 1. Consort diagram showing the study populations stratified by disease state. CP, chronic pancreatitis; NAPS2, North American Pancreatitis Study 2; RAP, recurrent acute pancreatitis.

established MBD and CP association, this pilot study aimed to investigate a panel of circulating bone metabolism biomarkers reflective of bone remodeling processes in RAP and CP subjects, focusing on differential expression across disease stages. Secondarily, we aimed to investigate the association between these markers, disease stage, and sex, and evaluate modifiable lifestyle factors (e.g., alcohol and tobacco use).

Given the exploratory nature of this study, our findings underscore the need for larger-scale investigations (e.g., validation in the prospective, longitudinal PROCEED study (29)), to advance mechanistic understanding and guide targeted interventions for pancreatitis-associated bone loss. The goal is to identify candidate biomarkers that reflect underlying shifts in bone metabolism in patients with pancreatitis. Extensive evaluation of biochemical bone metabolism markers is essential to clarify mechanisms underlying bone health deterioration and identify biomarkers that signal early imbalance or transition in pancreatitis-associated bone disease.

METHODS

Study population

The NAPS2 consortium prospectively enrolled subjects at 20 different US sites between 2000 and 2014 (30). The study population consisted of subjects enrolled in NAPS2 (refer to Figure 1) including CP (n = 40), RAP (n = 40), and controls (n = 30). RAP was defined as having 2 or more confirmed AP with no definitive evidence of CP; CP was defined based on definitive evidence primarily from cross-sectional imaging (CT scan and/or MRI/magnetic resonance cholangiopancreatography) or histology.

Informed consent was given by all subjects enrolled and approved by the Institutional Review Board of each site in the NAPS2 consortia.

Samples

Samples were collected from subjects enrolled in the NAPS2 study, and serum was isolated from whole blood by centrifugation and stored at −80 °C until analyzed. All serum samples were shipped on dry ice and blindly analyzed. Sample aliquots were allowed to thaw only once, just before analysis. Study group sizes (N) were fixed (based on the number of samples provided by the NAPS2 consortia); therefore, no formal power calculation was performed.

Serum protein analysis

Ten serum proteins were chosen as markers of bone remodeling for inclusion in a customized commercially available MILLIPLEX MAP Human Bone Magnetic Bead Panel-Bone Metabolism Multiplex Assay (Millipore Sigma, Burlington, MA). Analytes included mechanistic markers (sclerostin, dickkopf-1 [DKK1], receptor activator of nuclear factor κβ ligand [RANKL], and osteoprotegerin [OPG]), hormonal regulators (fibroblast growth factor 23 [FGF23], insulin, and leptin), and modulatory markers (osteopontin, oncostatin, and osteoactivin). The calculated ratio of RANKL to OPG was used as an additional remodeling indicator. Assays performed according to the manufacturer's protocol using Luminex MAGPIX Multiplex. One subject sample (RAP) was removed from the marker analyses because of a problem with sample loading (no data generated).

Statistical analysis

Study subject characteristics were compared among disease groups: control, RAP, and CP. Categorical variables were summarized by frequency (n) and proportion (%), while continuous variables were summarized by mean and standard error (SE). *P* values were calculated using one-way ANOVA and the Fisher's exact test for continuous and categorical variables, respectively. A *P* value <0.05 was considered significant. Any missing data were excluded and noted.

Mean differences in bone biomarkers among the disease stage groups were compared using 1-way ANOVA. Data distributions were examined; for normalization of right-skewed markers, log transformations were applied before analysis. The false discovery rate method was used to adjust ANOVA *P* values for multiple testing. For statistically significant ANOVA tests, pairwise comparisons were performed with Tukey adjustments controlling familywise error rate. Assumptions of normality and homogeneity were assessed before conducting pairwise comparisons. Primary analyses assessed unadjusted differences in bone biomarkers across pancreatic disease stages as an exploratory, hypothesis-generating assessment.

Secondary analyses evaluated adjusting for demographic and clinical confounders. Multivariable linear regression models were used to identify independent predictors (or factors) of serum bone marker levels; however, assumption violations prevented reliable covariate (confounder) adjustment. Alternatively, backward stepwise linear regression was performed with variable selection (final models) based on the lowest Akaike Information Criterion. Factors included in full model were disease diagnosis, age, sex, race, body mass index (BMI), alcohol use, and tobacco use. Interaction terms included were age by sex and race by sex. Residual plots were generated to assess linearity; the Breusch-Pagan and nonconstant variance tests assessed homogeneity; Q-Q plots and Shapiro-Wilk tests evaluated normality of residuals. Generalized variance inflation factors were calculated to assess multicollinearity; factors with generalized variance inflation factor >5 were excluded. Positive parameter estimates (coefficients) suggest elevated levels, whereas negative parameter estimates suggest reduced levels compared with the reference group. Overall model performance was evaluated using adjusted R^2 values.

Stratified (subgroup) analyses by sex, smoking status, or drinking status were conducted using ANOVA because parametric assumptions were violated. If assumptions of normality or homogeneity were violated, the nonparametric Kruskal-Wallis test was used. For statistically significant Kruskal-Wallis tests, post hoc pairwise comparisons were conducted using the Dunn test with Bonferroni adjustment for multiple comparisons.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R Project software (version 4.2.2) (31,32).

Editorial assistance

After completion of the prefinal draft, editorial assistance was provided by ChatGPT (OpenAI, San Francisco, CA), an artificial intelligence language model, to improve grammar, clarity, and readability of the manuscript. All scientific content, data interpretation, and final edits were independently reviewed and approved by the authors to ensure accuracy and integrity.

Table 1. Baseline characteristics of study subjects

Characteristic	Controls (n = 30)	RAP subjects (n = 40)	CP subjects (n = 40)	*P* value
Sex				0.86
Male	16 (53.3)	24 (60.0)	24 (60.0)	
Female	14 (46.7)	16 (40.0)	16 (40.0)	
Age	54.1 (1.6)	50.8 (1.4)	53.5 (1.4)	0.21
Race				0.11
White	30 (100.0)	37 (92.5)	40 (100.0)	
African American	—	3 (7.5)	—	
BMI				
BMI (lbs/in^2)	29.17 (1.1)	29.97 (1.0)	25.76 (1.0)	<0.01
BMI <25	3 (10.0)	10 (25.0)	22 (55.0)	<0.01
BMI ≥25	27 (90.0)	30 (75.0)	18 (45.0)	
Smoking status				<0.01
Nonsmoker	8 (26.7)	13 (32.5)	9 (22.5)	
Past smoker	16 (53.3)	12 (30.0)	12 (30.0)	
Current smoker	6 (20.0)	15 (37.5)	19 (47.5)	

Values presented as mean (SE) or n (%).
BMI, body mass index; CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

RESULTS

Study population and subject characteristics

A total of 110 subjects were included in the study: 30 controls, 40 RAP subjects, and 40 CP subjects (Figure 1). Detailed demographic and clinical characteristics are summarized in Tables 1 and 2. The groups were similar for sex, age, and race. However, a significant difference in BMI was observed across groups ($P < 0.01$), with a significant association between BMI category and disease stage ($P < 0.01$). As anticipated, among subjects with RAP and CP, significant associations were identified for smoking status ($P < 0.01$), drinking status ($P < 0.01$), and exocrine pancreatic insufficiency ($P = 0.02$). No significant differences were observed in patterns of pain among the study groups. Although there was no significant association among subjects in the RAP or CP groups with medication use for pain, 90% (72/80) of these subjects reported a history of abdominal pain at baseline. Tobacco (smoking status) and alcohol use (status) patterns varied markedly by sex and study group, with CP subjects—especially males—being mostly current smokers and heavy to very heavy drinkers (see Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/B396).

Mechanistic markers of bone remodeling: sclerostin, DKK1, RANKL, and OPG

Serum levels for all 4 mechanistic markers were significantly increased in RAP and CP subjects compared with controls (Figure 2a–d and Table 3), with a greater elevation observed in CP. The ratio of RANKL to OPG levels (RANKL/OPG) is often used as an indicator of bone turnover: RANKL has a stimulatory effect on bone resorption, while OPG is inhibitory to RANKL (33). The ratio of RANKL/OPG (data not shown) was significantly elevated in CP compared with RAP subjects and controls ($P < 0.01$).

Serum levels for sclerostin, DKK1, and RANKL were also found to be significantly different in subjects with pancreatitis compared with controls when stratified by sex (see Table 3, Supplementary Digital Content 3, http://links.lww.com/CTG/B398) and by smoking (see Table 4, Supplementary Digital Content 4, http://links.lww.com/CTG/B399) or drinking status (see Table 5, Supplementary Digital Content 5, http://links.lww.com/CTG/B400).

Hormonal regulators of bone remodeling processes: FGF23, insulin, and leptin

Serum FGF23 levels were significantly elevated in RAP subjects (Figure 3a and Table 4), insulin levels were significantly lower in CP subjects compared with controls (Figure 3b), particularly in men (see Table 3, Supplementary Digital Content 3, http://links.lww.com/CTG/B398), whereas no significant differences were identified for leptin (Figure 3c).

Insulin and leptin had significantly different serum levels when stratified by sex (see Table 3, Supplementary Digital Content 3, http://links.lww.com/CTG/B398) and by smoking status (see Table 4, Supplementary Digital Content 4, http://links.lww.com/CTG/B399). These findings suggest that serum levels of hormonal regulators associated with bone remodeling processes are altered in subjects with pancreatic disease with further variability based on sex and tobacco use.

Modulators of bone remodeling: osteopontin, oncostatin, and osteoactivin

Serum osteopontin levels were significantly elevated in CP subjects compared with RAP and control subjects (Figure 4a

Table 2. Clinical characteristics of study subjects with pancreatitis

Characteristic n (%)	RAP subjects (n = 40)	CP subjects (n = 40)	*P* value
Exocrine insufficiency			0.02
Yes	5 (12.5)	15 (37.5)	
No	35 (87.5)	25 (62.5)	
Endocrine insufficiency			1.00
Yes	20 (50.0)	20 (50.0)	
No	20 (50.0)	20 (50.0)	
Pain pattern[a]			0.17
No pain	2 (5.0)	6 (15.0)	
Usually pain-free, but with episodes of mild-moderate pain	5 (12.5)	6 (15.0)	
Constant mild-moderate pain	1 (2.5)	2 (5.0)	
Usually free of abdominal pain, but with episodes of severe pain	17 (42.5)	8 (20.0)	
Constant mild-moderate pain plus episodes of severe pain	15 (37.5)	16 (40.0)	
Constant severe pain	0 (0.0)	2 (5.0)	
Pain medication use			0.17
No pain medication	20 (50.0)	14 (35.0)	
Nonnarcotic medication	2 (5.0)	0 (0.0)	
Intermittent narcotics	13 (32.5)	16 (40.0)	
Constant narcotics	5 (12.5)	10 (25.0)	
Drinking status[b]			<0.01
Abstainers	9 (22.5)	7 (17.5)	
Light-moderate drinkers	18 (45.0)	9 (22.5)	
Heavy-very heavy drinkers	13 (32.5)	24 (60.0)	
Alcohol etiology			<0.01
Yes	3 (7.5)	22 (55.0)	
No	37 (92.5)	18 (45.0)	

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.
[a]Excluded controls: abstainers (n = 29), heavy-very heavy (n = 1).
[b]Based on pain experience in the year before enrollment.

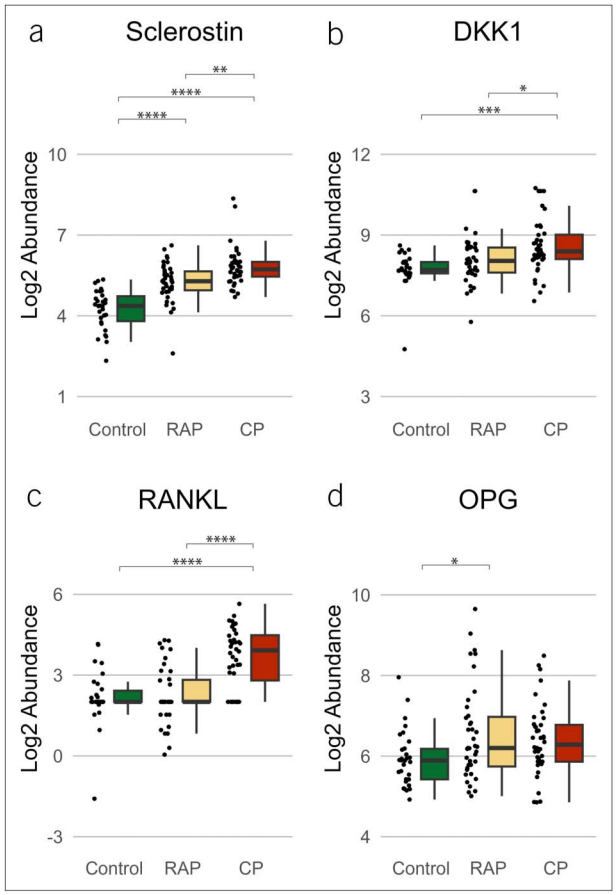

Figure 2. Mechanistic markers of bone remodeling in serum samples from RAP and CP subjects. Box and dot plots show the levels for mechanistic markers associated with bone turnover for all 3 groups. Sclerostin (**a**), DKK1 (**b**), RANKL (**c**), and OPG (**d**) levels were identified statistically as significantly increased in the serum samples ($*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$). CP, chronic pancreatitis; DKK1, dickkopf-1; NAPS2, North American Pancreatitis Study 2; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κβ ligand; RAP, recurrent acute pancreatitis.

and Table 5). In addition, osteopontin levels in RAP subjects were also significantly higher compared with controls. Serum oncostatin levels in CP subjects were also significantly elevated compared with controls (Figure 4b). No significant differences were found for osteoactivin levels between the groups (Figure 4c).

Osteopontin was the only modulatory marker to also have significantly different serum levels when stratified by sex (see Table 3, Supplementary Digital Content 3, http://links.lww.com/CTG/B398) and by smoking (see Table 4, Supplementary Digital Content 4, http://links.lww.com/CTG/B399) or drinking status (see Table 5, Supplementary Digital Content 5, http://links.lww.com/CTG/B400). These findings are in agreement with other clinical studies identifying sex differences in serum levels of osteopontin (34).

Impacts of pancreatic disease state and other factors on circulating bone biomarkers

We conducted a comparative analysis of bone biomarkers across the study groups (control vs RAP, control vs CP, RAP vs CP), visualizing their overlapping distribution through a Venn diagram (Figure 5). Sclerostin and osteopontin were the only markers that significantly distinguished all 3 groups, consistent with their central role(s) in bone metabolism, and highlighting the dysregulation underlying MBD in pancreatitis. DKK1 and RANKL differentiated CP from RAP and controls, further supporting their involvement in advanced pancreatitis disease stages. The remaining biomarker differences underscore distinct yet overlapping mechanisms of bone remodeling at different stages of pancreatic disease progression.

Multivariable linear regression using stepwise variable selection was used to evaluate the effect of pancreatic disease stage (RAP or CP) and other factors on individual serum bone biomarkers (see Table 2, Supplementary Digital Content 2, http://links.lww.com/CTG/B397). Model performance varied considerably across bone markers and predictor variable inclusion. Disease diagnosis was

Table 3. Mechanistic markers of bone remodeling among study subjects

	Sclerostin	DKK1	RANKL	OPG
Study group				
Controls	4.4 (3.8–4.7)	7.7 (7.6–8.0)	2.0 (2.0–2.4)	5.9 (5.4–6.2)
RAP	5.3 (5.0–5.7)	8.0 (7.6–8.5)	2.0 (2.0–2.8)	6.2 (5.7–7.0)
CP	5.7 (5.5–6)	8.4 (8.1–9.0)	3.9 (2.8–4.5)	6.3 (5.9–6.8)
Group comparisons				
Controls vs RAP	0.4 (0.2–0.6)[c]	NS	NS	0.5 (0.3–0.8)[b]
Controls vs CP	4.9 (3.2–7.4)[c]	2.4 (1.4–3.9)[b]	4.4 (2.4–8.1)[c]	NS
RAP vs CP	1.8 (1.2–2.6)[b]	1.6 (1.0–2.6)[a]	4.1 (2.3–7.3)[c]	NS

Values presented as median (interquartile range) or LSM difference (95% confidence interval).
CP, chronic pancreatitis; DKK1, dickkopf-1; LSM, least squares means; NAPS2, North American Pancreatitis Study 2; NS, not significant; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κβ ligand; RAP, recurrent acute pancreatitis.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.0001$.

identified as significant for predicting the serum levels of several mechanistic markers and modulators. Specifically, RAP and CP associated with higher sclerostin and DKK1, while only CP associated with higher RANKL and osteopontin suggesting these markers may be more directly influenced by pancreatitis-associated pathophysiological mechanisms. Other biomarkers seemed to be more strongly associated with demographic and lifestyle factors. Age showed positive associations with OPG and osteoactivin; higher leptin was associated with men and subjects with higher BMI. The association between diagnosis and several of the markers (FGF23, insulin, leptin, oncostatin, and osteoactivin) was not strong enough to warrant inclusion in the regression model when the other variables were present, suggesting these may better explain the variances between study groups.

DISCUSSION

This exploratory pilot study of the NAPS2 Study provides the most comprehensive evaluation to date of serum bone metabolism markers across stages of pancreatitis. Although clinical evidence links pancreatitis with MBD, limited studies have evaluated the underlying pathophysiological mechanisms. By examining a panel of bone remodeling markers in subjects with RAP and CP, we identified candidates potentially linking pathological processes of MBD in subjects with pancreatitis. This study expands on prior findings by uncovering metabolic changes associated with bone remodeling in these patients, beyond what is routinely used clinically or what has been previously shown. The findings highlight a clear relationship between CP and changes in mechanistic markers of bone remodeling, as evidenced by elevated levels of sclerostin, DKK1, RANKL, and OPG. Distinct shifts in bone metabolism were observed across disease stages suggesting an imbalance in bone remodeling resulting in temporal bone loss. Understanding these patterns of imbalance may provide insight into potential therapeutic targets for mitigating bone loss in patients with pancreatitis.

These observations align with previous epidemiological studies linking CP to a higher prevalence of osteopathy and fragility fractures (35). In a previous study based on the NAPS2 cohort, we found that CP was associated with significantly lower

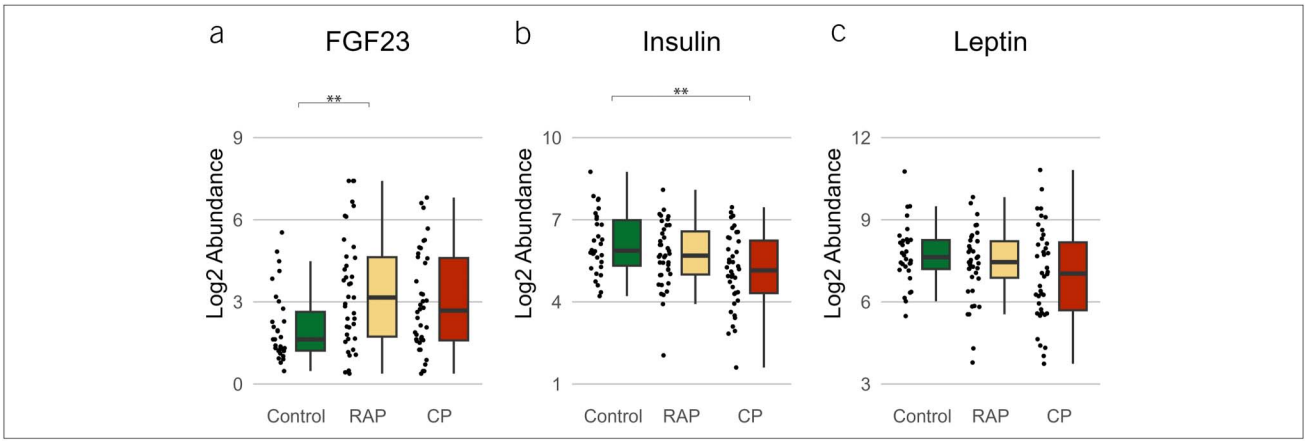

Figure 3. Hormonal regulators of bone remodeling in serum samples from RAP and CP subjects. Box and dot plots show the levels across all 3 groups for regulatory markers associated with bone remodeling. Statistical analyses identified differences as follows: FGF23 levels (**a**) were significantly higher in the subject serum samples in the RAP group compared with controls (**$P < 0.05$); insulin levels (**b**) were significantly lower in the CP group compared with controls (**$P < 0.01$); differences in leptin levels (**c**) among the groups were insignificant. CP, chronic pancreatitis; FGF23, fibroblast growth factor 23; RAP, recurrent acute pancreatitis.

Table 4. Hormonal regulators of bone remodeling among study subjects

	FGF23	Insulin	Leptin
Study group			
Controls	1.6 (1.2–2.64)	5.9 (5.3–7.0)	7.6 (7.2–8.3)
RAP	3.2 (1.7–4.6)	5.7 (5.0–6.6)	7.5 (6.9–8.2)
CP	2.7 (1.6–4.6)	5.2 (4.3–6.2)	7.0 (5.7–8.2)
Group comparisons			
Controls vs RAP	0.3 (0.1–0.8)[a]	NS	NS
Controls vs CP	NS	0.4 (0.2–0.8)[a]	NS
RAP vs CP	NS	NS	NS

Values presented as median (interquartile range) or LSM difference (95% confidence interval).
CP, chronic pancreatitis; FGF23, fibroblast growth factor 23; LSM, least squares mean; NS, not significant; RAP, recurrent acute pancreatitis.
[a]$P < 0.01$.

levels of osteocalcin (a measure of osteoblast activity during bone formation) and significantly higher C-reactive protein levels when compared with controls, suggesting that CP subjects had increased systemic inflammation and bone remodeling (36).

Bone remodeling processes are regulated by cellular signaling pathways that maintain the balance between bone formation and resorption (loss). Resorption is primarily driven by osteoclasts, largely through RANKL/RANK signaling (37–39). RANKL, a proinflammatory cytokine, plays a key role in promoting this process (37,40,41). Alternatively, bone resorption can also result from bone formation suppression by sclerostin (42) and/or DKK1 (43) both of which modulate the Wnt signaling (44), a critical signaling pathway for bone formation. OPG acts as a decoy receptor thereby interfering with RANKL/RANK binding (45). The RANKL/OPG ratio is critically important for regulating bone remodeling (35,41). The stepwise increases in sclerostin, DKK1, and RANKL levels in RAP and CP subjects point to distinct mechanistic shifts in bone remodeling, possibly implicating both enhanced osteoclastogenesis and impaired osteoblast activity in the development of MBD in patients with pancreatitis. Similarly, the elevation of the RANKL/OPG ratio in RAP and CP subjects further implicates enhanced bone resorption in patients with pancreatitis. The identification of distinct bone marker profiles between RAP and CP also suggests that bone turnover abnormalities may evolve with disease stage progression. Although subjects with RAP exhibited increased OPG levels, potentially reflecting an initial compensatory response to increased bone resorption, subjects with CP demonstrated significantly higher markers of osteoclast activity, indicating a shift toward pathological bone loss. Insulin and leptin (46) are key hormonal regulators of bone formation and remodeling—albeit through direct and indirect mechanisms of action—with insulin playing a key role. Through its receptor on osteoblasts (47), insulin reduces OPG levels, thereby enhancing RANKL-mediated bone resorption. In this way, insulin contributes to both bone formation and resorption, linking skeletal remodeling to glucose homeostasis (48,49). The observed reduction in serum insulin levels in CP subjects may indicate impaired osteoblast function and disrupted bone remodeling, highlighting the broader impact of pancreatic endocrine dysfunction on bone health.

Osteopontin, a proinflammatory cytokine involved in a range of physiological processes (50), has been associated with numerous chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and osteoporosis (51,52). In our study, osteopontin levels increased stepwise across RAP and CP subjects, supporting its potential as a mechanistic biomarker for MBD in pancreatitis. In addition, we observed significant gender differences in osteopontin levels at different stages of pancreatitis, consistent with prior clinical studies reporting sex-based variations in circulating osteopontin (34). FGF23 and oncostatin, both involved in regulating bone remodeling, were also elevated. FGF23 plays a role in phosphate metabolism and bone mineralization (53–55), while oncostatin has been implicated in

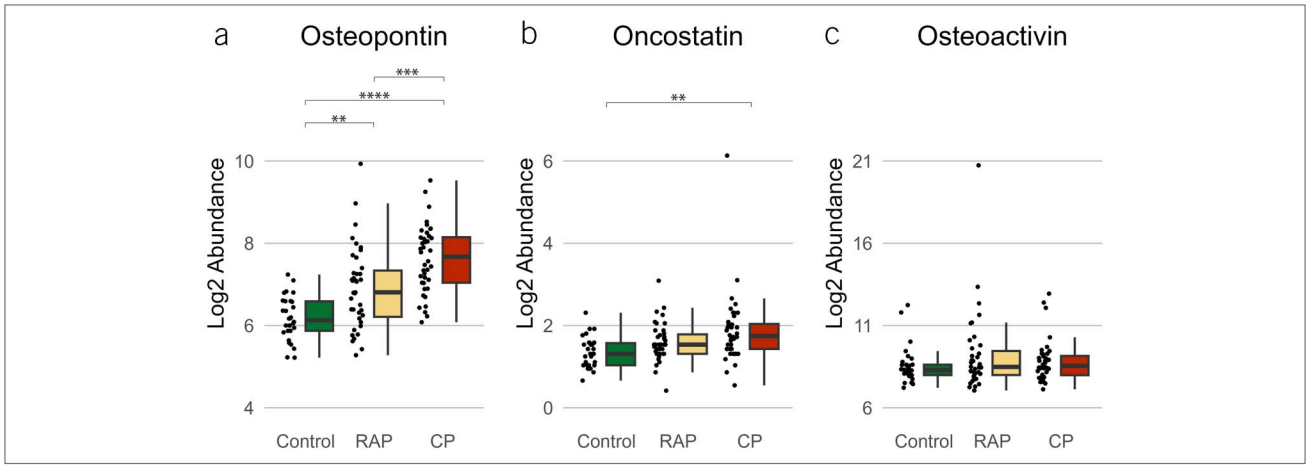

Figure 4. Modulators of bone remodeling in serum samples from RAP and CP subjects. Box and dot plots show the levels for modulatory markers of bone remodeling for all 3 groups. The osteopontin (**a**) and oncostatin (**b**) levels were identified statistically as significantly increased in the serum samples (**$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$). Differences in osteoactivin levels (**c**) among the groups were insignificant. CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

Table 5. Modulators of bone remodeling among study subjects

	Osteopontin	Oncostatin	Osteoactivin
Study group			
Controls	6.1 (5.9–6.6)	1.3 (1.0–1.6)	8.3 (8.0–8.6)
RAP	6.8 (6.2–7.3)	1.5 (1.3–1.8)	8.5 (8.0–9.5)
CP	7.7 (7.0–8.2)	1.7 (1.4–2.0)	8.6 (8.0–9.2)
Group comparisons			
Controls vs RAP	0.5 (0.3–0.8)[a]	NS	NS
Controls vs CP	4.2 (2.6–6.8)[b]	1.7 (1.2–2.4)[a]	NS
RAP vs CP	2.0 (1.3–3.2)[a]	NS	NS

Values presented as median (interquartile range) or LSM difference (95% confidence interval).
CP, chronic pancreatitis; LSM, least squares means; NS, not significant; RAP, recurrent acute pancreatitis.
[a]$P < 0.01$.
[b]$P < 0.0001$.

osteoclast and osteoblast regulation (56–58). Leptin, a hormone associated with bone formation, has also been shown to influence FGF23 activity (59). These findings suggest that alterations in these hormonal regulatory pathways may contribute to the imbalanced bone turnover observed in pancreatitis, highlighting their potential as mechanistic biomarkers.

Given the known morbidity associated with osteoporosis and fractures, the identification of mechanistic biomarkers of bone metabolism dysregulation has significant prognostic and therapeutic implications. This study highlights the clinical potential of mechanistic bone markers in pancreatitis and aims to provide mechanistic understanding of bone loss across disease stages, rather than inform differential diagnosis. The significant differences in sclerostin, osteopontin, and the RANKL/OPG ratio suggest that these markers could serve as valuable clinical indicators of underlying metabolic dysfunction or dysregulation. The identification of key signaling pathways could thus be used for assessing and monitoring bone health in patients with pancreatitis.

These findings provide strong rationale for further investigation into relationships between the calcium-vitamin D-parathyroid axis, weight loss, and kidney function in pancreatitis-associated MBD. Understanding the temporal relationships between pancreatitis disease and MBD will help identify stage-specific mechanisms and inform clinical practice to improve patient outcomes. This pilot study serves as a foundation to evaluate bone remodeling biomarkers in larger studies while accounting for concurrent pathological processes and potential confounders. The PROCEED study (29), a large, prospective, longitudinal study, represents an opportunity to expand and validate these results.

Identified and validated mechanisms can also be used for developing targeted pharmacological (60), nutritional, and/or therapeutic interventional strategies. Targeted clinical interventions, such as the administration of sclerostin inhibitors (such as romosozumab) (61) to mitigate bone loss in patients with pancreatitis, should also be explored to counteract bone loss in patients with pancreatitis exhibiting suppressed bone formation. The eventual incorporation of bone turnover markers into clinical evaluation may enable a more personalized treatment approach. For example, mechanistic biomarkers may help clinicians determine whether a patient's bone loss is driven primarily by increased resorption, impaired formation, or both, thereby guiding the selection of targeted therapies.

Limitations of this study include sample size, cross-sectional design, and nonavailability of clinical laboratory data (liver and kidney markers/function). However, evaluating the association of alterations in these bone markers with different stages of pancreatic disease provides a more mechanistic perspective as opposed to relating it to MBD providing a more phenotypic perspective. Given the small sample size of this pilot study, we were unable to clearly define subtypes of patients based on the results of the bone panel. The absence of covariate adjustment is a key limitation because factors such as age, sex, smoking, alcohol use, and pancreatic dysfunction (endocrine and/or exocrine) are known to influence both pancreatitis and bone metabolism. However, the similar distributions for age and gender distributions ($P > 0.05$) suggest that group differences in these bone biomarkers are less likely to be attributable to these confounders. In addition, the use of stepwise variable selection represents an exploratory approach with known limitations, including potential overfitting and inflated significance levels. These results should be interpreted cautiously and require replication/validation in future studies. Another important limitation is the inability to correlate serum marker changes with BMD data because dual-energy x-ray absorptiometry scans were only available for a limited number of NAPS2 subjects; future studies should include data

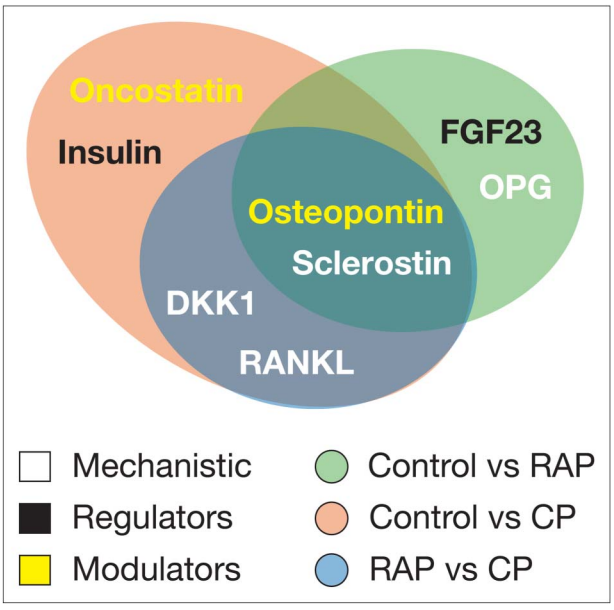

Figure 5. Significant bone remodeling marker interactions by type and group. The Venn diagram shows the significant bone markers that are shared or uniquely involved in each intersection set. Combinations of bone biomarker proteins are shown grouped by significant comparisons. Sclerostin and osteopontin are shared by all 3 sets. CP, chronic pancreatitis; DKK1, dickkopf-1; FGF23, fibroblast growth factor 23; NAPS2, North American Pancreatitis Study 2; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κβ ligand; RAP, recurrent acute pancreatitis.

from patients with dual-energy x-ray absorptiometry results and fracture history.

In conclusion, this study represents the most comprehensive evaluation of biomarkers involved in bone remodeling in subjects with pancreatitis to date, providing novel mechanistic insight into the pathophysiology of pancreatitis-associated osteopathy. Understanding mechanisms underlying bone metabolism alterations may ultimately inform precision medicine approaches to prevent osteoporosis and reduce fracture risk in this vulnerable population.

CONFLICTS OF INTEREST

Guarantor of the article: Rachel L. Hill, PhD, MS.

Specific author contributions: R.L.H.: conceptualization—equal, investigation—equal, project administration and management—lead, formal analysis—equal, visualization—lead, manuscript writing—lead, manuscript review and editing—equal. D.C.W.: funding acquisition—lead. K.J.M.: project administration and management—supporting, formal analysis—lead, manuscript review and editing—supporting, visualization—supporting. K.N.K.: formal analysis—supporting, visualization—supporting, manuscript review and editing—supporting. D.L.C.: conceptualization—lead, investigation—equal, funding acquisition—lead, manuscript writing—supporting, manuscript review and editing—equal. M.R.: visualization—supporting, manuscript writing—supporting, manuscript review and editing—equal. All authors critically evaluated, revised, and approved the final version of this manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ Chronic pancreatitis is associated with reduced bone mineral density and elevated fragility fracture risk.
- ✓ Patients with pancreatic disease are often underscreened for bone density loss.
- ✓ Both nonmodifiable (genetic, biological) and modifiable (lifestyle, environmental) factors influence bone health.
- ✓ Bone remodeling is regulated by complex systemic and local signaling pathways.
- ✓ Dysregulated bone metabolism is integral to the pathophysiology of metabolic bone disease(s).

WHAT IS NEW HERE

- ✓ This study evaluates the largest mechanistic bone biomarkers panel in recurrent acute pancreatitis and chronic pancreatitis to date.
- ✓ Multiple components of bone remodeling pathways are significantly altered in pancreatic disease.
- ✓ Progressive, stage-specific changes in bone biomarkers indicate active and imbalanced remodeling with disease severity.
- ✓ Serum bone biomarker profiles may guide early detection, clinical management, and mechanistic research.
- ✓ Metabolic shifts in bone remodeling may guide early detection and targeted interventions in patients with pancreatitis.
- ✓ Serum bone biomarker profiles inform mechanistic and translational research aimed at improving patient outcomes.

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