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The Impact of Exocrine Pancreatic Insufficiency in Patients with Chronic Pancreatitis on Bone Health - a Literature Review

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ABSTRACT

Background. Chronic pancreatitis is described as irreversible damage to the pancreas leading to endocrine and exocrine dysfunction.
Exocrine pancreatic insufficiency (EPI) results in maldigestion and malabsorption of nutrients that is associated with developing osteopenia and osteoporosis that elevates bone fragility and puts patients at higher risk of higher low fracture rates.

Aim. This review aims to outline current evidence on the pathophysiological mechanism, prevalence, risk factors and clinical implications of osteoporosis in patients with EPI secondary to chronic pancreatitis.

Material and methods. A comprehensive literature search was performed using electronic databases (including PubMed, Web of Science, and ClinicalKey), to identify studies examining osteoporosis in patients with chronic pancreatitis. Searches were performed using relevant keywords and combinations such as “chronic pancreatitis,” “exocrine pancreatic insufficiency,” “osteoporosis,” “osteopenia,” and “bone mineral density.” Studies published in English were considered. Manual screening of references from all included studies was performed to locate further relevant studies

Extracted data were synthesized qualitatively using a literature review approach, focusing on prevalence, risk factors, pathophysiology, and clinical outcomes related to bone health in this population.

Conclusion. Patients with chronic pancreatitis and long-term exocrine pancreatic insufficiency frequently display reduced bone mineral density, resulting in increased osteoporosis risk and fragility fractures. Enzyme therapy should be provided to improve nutrient absorption. Further research is needed to precisely determine fracture-related morbidity and mortality in this population.

Key words: osteoporosis, chronic pancreatitis, exocrine pancreatic insufficiency, osteopenia

Chronic Pancreatitis

Chronic pancreatitis is a progressive fibro-inflammatory disease of the pancreas which is determined by irreversible damage that occurs in individuals with inherent or acquired risk factors who present sustained pathological responses after pancreatic stress or injury.
As chronic pancreatitis advances, permanent remodeling of pancreatic tissue occurs, marked by atrophy and fibrosis, frequently leading to chronic pain manifestations (Luo et al., 2025).

It leads to loss of functional pancreatic tissue causing exocrine pancreatic insufficiency (EPI) and endocrine pancreatic dysfunction, and in some cases, epithelial dysplasia (Thierens et al., 2024).
The pathogenesis of chronic pancreatitis involves several interacting factors. Persistent alcohol consumption and smoking are the most frequently observed risk factors. Metabolic causes such as hypertriglyceridemia and hypercalcemia are additionally involved in (Hansen et al., 2023).
A history of acute pancreatitis in the past increases the risk of progression to chronic disease (Sankaran et al., 2015).
Mutations in PRSS1, SPINK1, and CTRC represent critical genetic risk factors, promoting improper trypsinogen activation or impairing its breakdown, which contributes to pancreatic damage (Singh et al., 2019).
A well-established etiological classification system is the TIGAR-O classification (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, obstructive), later modified to TIGAR-O2 to incorporate updated mechanistic insights (Etemad & Whitcomb, 2001).
Current evidence demonstrates a marked rise in the incidence of chronic pancreatitis. A population-based study noted a near-doubling of cases, rising up to 8,27 per 100 000 annually within just seven years. Factors contributing to this trend include an older population, improvements in diagnostic modalities such as EUS and MRCP, and elevated metabolic risk profiles (Cai et al., 2023).
As chronic pancreatitis progresses, the onset of exocrine pancreatic insufficiency (EPI) is expected in most cases, affecting approximately 80% of patients within 10 to 12 years of clinical diagnosis (Thibonnier & Ghosh, 2023). As a result, the frequency of chronic, long-term complications of chronic pancreatitis will likely rise.
Progressive impairment of the exocrine function results in a massive cohort of patients at high risk for secondary metabolic bone disease. Studies indicate that more than 25% of this

population already suffers from osteoporosis, while an additional 40% is exhibiting osteopenia (Hurley et al., 2020).

Exocrine pancreatic insufficiency

Exocrine Pancreatic Insufficiency (EPI) is a clinical condition characterized by a deficiency of pancreatic enzymes (lipase, protease, and amylase) and bicarbonate, which are crucial for proper digestion. This results in not sufficient breakdown and absorption of nutrients, leading to malnutrition and suboptimal levels in key vitamins and minerals. It is caused by pancreatic parenchymal destruction, for example due to inflammation during chronic pancreatitis (Domínguez-Muñoz & Phillips, 2018).
Exocrine pancreatic insufficiency is one of the most common adverse outcome of chronic pancreatitis (Diéguez-Castillo et al., 2020).
In patients with chronic pancreatitis, exocrine pancreatic insufficiency is more likely with alcohol use, duct obstruction, pancreatic atrophy, calcifications, or type 3c diabetes (Whitcomb, Buchner, et al., 2023). Smoking is an independent risk factor for EPI in CP patients (Erchinger et al., 2022).

Diagnostic tests of pancreatic function allow accurate quantification of exocrine and ductal secretion. Direct tests, which measure pancreatic secretions into the duodenum after hormonal stimulation ensure optimal accuracy, but are associated with invasiveness, prolonged procedure times, and limited availability outside specialized institutions (Dominguez-Muñoz, 2018; Whitcomb, Duggan, et al., 2023).
Indirect tests are less complex, noninvasive, and more accessible. Fecal elastase-1 (FE-1) is the standard test, as its stability during intestinal passage permits stool levels to reflect exocrine pancreatic secretion.
FE-1 concentrations below 200 µg/g are regarded as abnormal, whereas levels under 100 µg/g are indicative of exocrine pancreatic insufficiency (Leeds et al., 2011).
The test is most reliable on formed or semi-formed stool. Excess fluid in stool specimens can compromise measurement accuracy, producing false-positive outcomes. Sensitivity for mild EPI is limited, and results may be repeated if indeterminate (Whitcomb, Buchner, et al., 2023).

Mechanisms of maldigestion and malabsorption

Efficient nutrient absorption is contingent upon adequate pancreatic enzyme secretion, correct luminal delivery, and favorable intraluminal conditions that permit complete enzymatic hydrolysis.
Exocrine pancreatic insufficiency impairs digestion of fats, proteins, and carbohydrates. Maldigestion with EPI can accompany almost all stages of chronic pancreatitis but is most prevalent in advanced stages (Othman et al., 2018).

Severe forms of EPI are presented by more serious features such as weight loss and steatorrhea and overall disruption of digestive processes (Löhr et al., 2017).
Fat malabsorption is a defining feature of EPI, it leads to weight loss and malnutrition and predisposing patients to deficiencies of fat-soluble vitamins, particularly A, D, E, and K (Greer et al., 2019).
Vitamin D and K deficiencies have been reported in 56% and 32% of patients with chronic pancreatitis. In the analyzed study, mean serum vitamin D levels were 20,2 ng/mL, and 56,4% of patients were classified as deficient (Stigliano et al., 2018).

Patients affected by EPI generally present with reduced BMI, with underweight status more common than in individuals with intact exocrine pancreatic activity. Studies indicate that malabsorption resulting from insufficient pancreatic digestive enzymes is likely the primary factor contributing to low body weight in chronic pancreatitis (Erchinger et al., 2022).
Impaired nutritional status in EPI promotes elevated risk of surgical complications and limits the healing process (Bundred et al., 2022).
EPI is associated also with a higher prevalence of sarcopenia (Olesen et al., 2019).
Individuals with EPI also tend to have higher HbA1C levels and CRP levels. Reduced serum concentrations of prealbumin, osteocalcin, magnesium, and retinol-binding protein are also observed (Greer et al., 2019; Diéguez-Castillo et al., 2020).
Complications related to the development of exocrine pancreatic insufficiency (EPI), as discussed previously raise the likelihood of mortality in patients (De La Iglesia-Garcia et al., 2018).

Bone Disease in Chronic Pancreatitis

Osteoporosis is a metabolic bone disease marked by the deterioration of bone microarchitecture and diminished bone mass, which significantly elevates the likelihood of sustaining fragility fractures (Qaseem et al., 2017). Worldwide, osteoporotic fractures, particularly those affecting the hip and vertebrae, carry a substantial burden of increased morbidity, mortality, and healthcare expenditures (Morin et al., 2025).

Diminished bone mineral density (BMD) is a well-documented complication of chronic gastrointestinal conditions that involve chronic diarrhea and nutrient malabsorption, (‘American Gastroenterological Association Medical Position Statement’, 2003).
However, despite these patients being vulnerable to bone loss, gastroenterologists frequently under-recognize and under-screen for this risk in routine clinical practice (Kanakis et al., 2020).
The clinical prevalence of metabolic bone disease in patients with chronic pancreatitis (CP) is strikingly high, with osteoporosis and osteopenia affecting approximately 19% and 37% of the population, respectively (Koh et al., 2023).
CP is associated with a notably high prevalence of low-trauma fractures. A large-scale cohort analysis revealed a fracture prevalence of nearly 5% within the CP population. This incidence is significantly elevated compared to healthy controls (1,1%). Furthermore, the fracture burden in CP is statistically comparable to that of other established high-risk gastrointestinal and hepatic disorders, including celiac disease and cirrhosis (Tignor et al., 2010).
The markedly increased risk of metabolic bone disease in patients with CP is driven by complex, multifactorial mechanisms with EPI serving as a principal pathophysiological mechanism. The decline in pancreatic enzyme secretion induces the maldigestion of dietary lipids, which in turn severely compromises the intestinal absorption of fat-soluble vitamins. Among these, profound deficiencies in vitamins D and K are particularly consequential, as both nutrients are indispensable for maintaining structural bone integrity and skeletal homeostasis (Stigliano et al., 2018).
Vitamin K deficiency contributes critically to skeletal fragility by impairing γ-carboxylation of osteocalcin, a process essential for proper bone matrix mineralization. This defect compromises bone strength directly (Zhang et al., 2025).
Emerging evidence indicates that vitamins D and K act synergistically, and their combined sufficiency is crucial for maintaining bone homeostasis (Van Ballegooijen et al., 2017).

The pathophysiological link between exocrine pancreatic insufficiency (EPI) and skeletal fragility involves disrupted nutrient signaling and altered bone homeostasis. Deficient serum 25-hydroxyvitamin D [25(OH)D] markedly impairs intestinal calcium absorption, leading to secondary hyperparathyroidism. Chronic elevation of parathyroid hormone (PTH) in turn accelerates bone resorption, resulting in progressive depletion of bone mineral density and increased fracture risk (Stigliano et al., 2018).
Sarcopenia, commonly observed in patients with EPI, further contributes to osteoporosis by reducing mechanical loading on bone, impairing osteoblast stimulation, and disrupting muscle-bone crosstalk, thereby accelerating bone loss and increasing fracture risk (Olesen et al., 2019).
Laboratory and imaging studies in CP patients frequently demonstrate elevated PTH and CRP, low serum 25-OHD, increased bone turnover markers (P1NP, OC, CTX-I), and abnormal BMD, reflecting a combination of increased bone resorption and impaired mineralization (Duggan et al., 2015; Kanakis et al., 2020).
Early identification and targeted management of modifiable factors, including exocrine pancreatic insufficiency, micronutrient deficiencies, inflammation, and adverse lifestyle exposures, are essential to mitigate osteoporosis progression, reduce fracture risk, and ultimately improve survival and quality of life (Parhiala et al., 2023).

Management Strategies

The primary goal in treating EPI is to ensure adequate lipid digestion to meet macronutritional and micronutritional needs, with a secondary goal of reducing steatorrhea and diet-related gastrointestinal symptoms.
After diagnosing EPI an integrated assessment by multiple specialists is recommended to examine the patient's digestive and endocrine function in combination with guidance from clinic dietitian and evaluation of patients overall health status (Domínguez-Muñoz & Phillips, 2018; Phillips et al., 2021).

Replacement therapy

Standard management of EPI primarily involves Pancreatic Enzyme Replacement Therapy (PERT). It represents the standard and highly effective approach for managing exocrine pancreatic insufficiency. Clinical studies have consistently demonstrated that initiation of PERT leads to significant improvements across multiple patient outcomes, including enhanced absorption of fats and proteins, gains in body weight and BMI. (Chu et al., 2024; De La Iglesia-García et al., 2017).
Therapy typically begins with 40.000-50.000 USP units administered during the primary meal. Adjustments can be made according to meal size and fat content. (Gardner et al., 2020; Phillips et al., 2021; Whitcomb, Duggan, et al., 2023).
Enzymes must be consumed alongside food to effectively facilitate nutrient breakdown, because their action targets the meal itself rather than pancreatic tissue (Layer et al., 2019). Proton pump inhibitors, when used alongside pancreatic enzyme therapy, can increase its effectiveness in selected patients (Löhr et al., 2017; Othman et al., 2018).
Studies indicate that up to 40% of pancreatic enzyme replacement therapy (PERT) are prescribed at doses below those recommended by European guidelines. While suboptimal dosing may partially relieve gastrointestinal symptoms, it is generally insufficient to ensure capable of achieving the intended nutritional support. Therefore, compliance with guideline-recommended doses and individualization of therapy is essential (Kadaj-Lipka et al., 2025).

However, even when administered at high doses, PERT formulations do not fully replicate native pancreatic secretion and may not completely resolve all clinical manifestations of exocrine pancreatic insufficiency (De La Iglesia-García et al., 2017).

Nutritional treatment

Dietary management should be individualized based on the severity of pancreatic disease and the level of exocrine insufficiency (De La Iglesia-García et al., 2017).
Systematic monitoring of nutritional status in response to PERT and tailored dietary strategies allows clinicians to optimize interventions and more effectively counteract malnutrition in affected individuals (Chu et al., 2024).
Multiple nutrient-rich meals should be offered to patients daily, and any detected deficiencies in fat-soluble vitamins or minerals should be corrected through supplementation (Olesen, 2024).

Treatment monitoring

Effective PERT is reflected by reduced symptoms, recovery of body weight, muscle mass and strength, and normalization of fat-soluble vitamin levels; monitoring stool patterns, nutritional status, vitamin levels, and muscle function provides valuable information on therapy adequacy (Domínguez-Muñoz & Phillips, 2018; Whitcomb, Buchner, et al., 2023).
Evaluation for diabetes, inflammation markers like CRP levels and diet should be considered as part of routine care (Whitcomb, Buchner, et al., 2023).
Measuring fecal elastase-1 (FE-1) remains valid even in patients receiving enzyme replacement therapy, although its sensitivity decreases in mild cases (Whitcomb, Buchner, et al., 2023; Olesen, 2024).
^{13}C-mixed triglyceride breath test permits evaluation of the response to enzyme replacement, although it requires more time to perform(Löhr et al., 2017).
Ongoing follow-up with careful monitoring of nutritional bone and pancreatic health, and function. Any emergence of unexplained weight loss or worsening abdominal discomfort warrants further diagnostic evaluation, while consistent advice on avoiding alcohol and tobacco remains a key part of care.

Treatment and screening of osteoporosis in EPI

Osteoporosis often remains asymptomatic until fractures occur, underscoring the need for early intervention to reduce fracture risk and associated complications. In individuals with chronic pancreatitis-related bone disease management should concurrently target bone health and pancreatic function.
It’s important to engage in regular resistance exercise, and provide adequate vitamin D and calcium intake, with supplementation for patients unable to meet requirements through diet alone.
Appropriately dosed pancreatic enzyme replacement therapy (PERT) is essential to optimize nutrient absorption, and when combined with nutritional support and physical activity, contributes to the prevention of vitamin deficiencies and supports bone integrity (Barkin & Barkin, 2020).
Interventions should be directed toward protecting remaining pancreatic tissue by addressing modifiable risk factors such as alcohol consumption and tobacco use (Duggan, 2017).
Bone Mineral Density (BMD) is quantified by the T-score, which measures a patient's deviation from peak young-adult bone mass. Diagnostic thresholds are stratified as follows: a T-score

of −1.0 or higher represents healthy bone preservation; values falling between −1.0 and −2.5 signal the onset of osteopenia; and any measurement at or below −2.5 confirms a clinical diagnosis of osteoporosis (LeBoff et al., 2022).
Osteoporosis is frequently underdiagnosed in chronic pancreatitis. DXA is performed in fewer than half of patients. Suboptimal monitoring leads to delayed diagnosis and increased fracture risk (Kanakis et al., 2020).
Bone health management is a non-negotiable pillar of chronic pancreatitis with EPI care. To proactively manage bone loss, bone mineral density (BMD) should be assessed using dual-energy X-ray absorptiometry (DXA) and repeated every 1-2 years (Duggan et al., 2014; Löhr et al., 2017; Domínguez-Muñoz & Phillips, 2018).

Conclusions

In exocrine pancreatic insufficiency, impaired digestion leads to steatorrhea, protein malabsorption, and sarcopenia, while deficiencies in fat-soluble vitamins D and K and minerals exacerbate bone fragility. The combination of sarcopenia and osteoporosis increases fracture risk. Osteoporosis in EPI is often asymptomatic until fractures occur, and PERT may fail to restore vitamin D and K pathways if doses are too low. Regular FE-1 tests and bone density assessment using DXA every 1-2 years is important to monitor bone health and guide preventive strategies. These findings underscore the need for further research on optimizing bone health, nutrition, and fracture prevention in chronic pancreatitis with EPI.

Disclosure

Author Contributions

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The authors declare no conflict of interest.

Declaration of the use of generative AI and AI
In preparing this work, the authors used Google Gemini for the purpose of improving language and readability. After using this tool, the authors reviewed and edited the content as necessary and accept full responsibility for the substantive content of the publication.

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