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Burden of bone disease in chronic pancreatitis: A systematic review and meta-analysis

Chhoda A *et al*. Bone disease and chronic pancreatitis

Ankit Chhoda, Maria Jose Hernandez-Woodbine, Nana Afua Akkya Addo, Syed Alishan Nasir, Alyssa Grimshaw, Craig Gunderson, Awais Ahmed, Steven D Freedman, Sunil G. Sheth

Abstract

BACKGROUND

Bone disease is an under-recognized cause of morbidity in chronic pancreatitis (CP). Over the past decade, publications of original studies on bone disease in CP has warranted synthesis of the evidence to ascertain the true burden of the problem.

AIM

To quantify the prevalence of osteopenia, osteoporosis and fragility fractures in CP patients and investigate the associated clinical features and outcomes.

METHODS

A systematic search identified studies investigating bone disease in CP patients from Cochrane Library, Embase, Google Scholar, Ovid Medline, PubMed, Scopus, and Web of Science, from inception until October 2022. The outcomes included prevalence of osteopenia, osteoporosis, and fragility fractures, which were meta-analyzed using a random-effects model and underwent metaregression to delineate association with baseline clinical features.

RESULTS

Twenty-one studies were included for systematic review and 18 studies were included for meta-analysis. The pooled prevalence of osteopenia and osteoporosis in CP patients was 41.2% (95%CI: 35.2%-47.3%) and 20.9% (95%CI: 14.9%-27.6%), respectively. The pooled prevalence of fragility fractures described among CP was 5.9% (95%CI: 3.9%-8.4%). Meta-regression revealed significant association of pancreatic enzyme replacement therapy (PERT) use with prevalence of osteoporosis [coefficient: 1.7 (95%CI: 0.6-2.8); $P < 0.0001$]. No associations with mean age, sex distribution, body mass index, alcohol or smoking exposure, diabetes with prevalence of osteopenia, osteoporosis or fragility fractures. Paucity of data on systemic inflammation, CP severity, and bone mineralization parameters precluded a formal meta-analysis.

CONCLUSION

This meta-analysis confirms significant bone disease in patients with CP. Other than PERT use, we observed no patient or study-specific factor to be significantly associated with CP-related bone disease. Further studies are needed to identify confounders, at-risk population, and to understand the mechanisms of CP-related bone disease and the implications of treatment response.

Key Words: Chronic pancreatitis; Fractures; Osteoporosis; Osteopenia; Bone disease

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Core Tip: Bone disease is an under recognized cause of morbidity in chronic pancreatitis (CP). This systematic review and meta-analysis demonstrate substantial burden of bone disease (osteopenia and osteoporosis) and fragility fractures in CP patients. In addition,

metaregression has demonstrated a significant association of osteoporosis with pancreatic enzyme replacement. The study is powered by high-quality studies with large sample size and clearly defined study population and outcome measures.

INTRODUCTION

Chronic pancreatitis (CP) is a progressive, multifactorial fibro-inflammatory syndrome, which arises from persistent pathological response to noxious stimuli[1]. It is characterized by chronic abdominal pain, exocrine and endocrine insufficiency. Over time, nutritional deficiencies, systemic inflammation, and etiological factors like alcohol or smoking may disrupt the balance between bone formation and resorption[2]. These maladaptive alterations may subsequently cause bone disease *i.e.*, osteopenia and osteoporosis, leading to fractures which result from low energy trauma, called fragility fractures, and have significant implications on quality of life[3].

Osteoporosis is a public health hazard with a substantial economic burden[4]. Recent data from the National Health and Nutrition Examination Survey found its age-adjusted prevalence among adults older than 50 years to be 12.6% affecting more women than men (19.6% *vs* 4.4%). In view of the burden of bone disease and subsequent fracture risk in individuals affected by CP, various consensus guidelines have recommended baseline bone health assessment[5,6]. The adherence to guidelines has been low and studies have demonstrated that less than a quarter of CP patients are screened for bone disease, suggesting that bone disease is an underappreciated source of morbidity in CP[7,8].

A previous systematic review by Duggan *et al*[9] estimated the prevalence of osteopenia and osteoporosis in patients with CP to be 39.8% and 23.4%, respectively. The analysis was based on a limited number of studies (n = 11) and did not quantify fragility fractures which are complications of CP-related bone disease. Over the last decade, multiple large-sized studies including those from multicenter cohorts have investigated bone disease in CP as well as the nutritional, anthropometric, and inflammatory parameters which may impact bone health outcomes. Thus, with quantitative data on covariates and fragility fractures available, an updated synthesis of evidence is pertinent. This systematic review and meta-analysis aim to quantify the prevalence of osteopenia, osteoporosis, and fragility fractures in CP patients and to delineate clinical parameters which impact their occurrence.

MATERIALS AND METHODS

Protocol registration

This systematic review was performed in accordance with PRISMA guidelines[10]. The review methodology was pre-registered at open-source forum[11].

Search strategy

A systematic search of the literature was conducted by a medical librarian in the following databases: Cochrane Library, Ovid Embase, Google Scholar, Ovid Medline, PubMed, Scopus, and Web of Science Core Collection to find articles published from the inception of the database to October 20, 2022. The search was performed using a combination of controlled and free text terms for CP and bone diseases (strategy outlined in Supplementary Table 1). The search was not limited to publication type or date. the search was peer-reviewed by a second librarian using peer review for electronic search strategies[12]. Citations were imported into an Endnote 20 Library (Version 20.2, Clarivate Analytics, Philadelphia), and after removal of duplicates, the remaining studies were imported into Covidence (Melbourne, Australia) for screening and data extraction.

Study selection

Two co-authors (MJ, AC) independently used the inclusion and exclusion criteria to assess titles and abstracts. Eligibility decisions and disagreements were reconciled through discussion with the senior author (SS). Full-text articles included by two reviewers underwent data extraction and quality assessment.

Inclusion criteria: This systematic review included original cross-sectional and cohort studies, which were of prospective and retrospective design. CP patients were diagnosed based on specific codes related to CP per the International Classification of Diseases (ICD-9/10) and through predefined clinical, radiologic and/or histologic findings (described in Table 1).

Exclusion criteria: The studies which did not report bone diseases in CP patients were ineligible for the systematic review. We also excluded studies published in foreign languages, associated with animal research, reviews, abstracts, letters, case reports, and series with a sample size of less than 10 patients were excluded (Figure 1).

Data extraction

We noted data on study design, population characteristics such as age, gender, method of CP diagnosis (ICD-code based *vs* systematic clinical-radiologic features), body mass index (BMI), and exposure to alcohol and smoking. These data were independently extracted by two authors (MJ and AC). The outcome of interest included the prevalence of osteopenia, osteoporosis, and fragility fractures among the CP patients. The definitions of these bone outcome measures were also noted and have been outlined in Table 2.

Meta-analysis methodology

Prevalence rates were pooled using random-effects meta-analysis and calculated using the score method[13]. Between-study heterogeneity was estimated using I^2 statistics wherein 25%, 50%, and 75% were considered to indicate low, moderate, and high heterogeneity, respectively. Sensitivity analysis was conducted by sequentially removing individual studies. Statistical analysis was performed using Stata/IC, version 17 (StataCorp, College Station, TX). Metaregression, subgroup analysis and publication bias assessment could not be performed for analyses including < 10 studies[14].

Metaregression

Metaregression using the restricted maximum likelihood method was also performed using variables of mean age, sex, BMI, smoking or alcohol exposure, diabetes, serum parathyroid hormone (PTH), percentage population with vitamin D deficiency, and pancreatic enzyme replacement therapy (PERT).

Study quality and publication bias assessment

The quality of observational studies was independently assessed using the Newcastle-Ottawa Scale by two investigators (SN and AA) and recorded in a Microsoft Excel spreadsheet (XP Professional Edition; Microsoft Corp, Redmond, WA, United States)[15]. Any discrepancy was resolved by the senior author (SS). Publication bias were assessed by inspection of a funnel plot and Egger's test[16].

RESULTS

Literature search

The literature search yielded 2081 results and after the removal of 20 duplicates, 2061 citations underwent title and abstract screening. The exclusion of 1979 citations due to lack of relevance to the research question resulted in 82 citations for full-text review. The review of their full texts enabled exclusion of 61 citations and finally 21 studies were included[17-37] (Supplementary Table 2). The excluded studies had incorrect study design (*n* = 27), wrong outcomes (*n* = 17), ineligible patient population (*n* = 8), non-English language (*n* = 6), wrong setting (*n* = 3), and duplicate center or overlapping populations (*n* = 1) (Supplementary Table 3). The search and selection processes are summarized in Figure 1.

Study design

All the eligible studies were observational studies and included 14 cross-sectional and 7 cohort studies (described in Table 1). Among the cohort studies, four were performed prospectively[25,26,31,33], and remaining three had retrospective design[34,36,37]. Most of the studies originated from European countries (*n* = 9), while the remaining were from the United States (*n* = 6), India (*n* = 4), China (*n* = 1), and Argentina (*n* = 1). Multicenter collaboration was noted in two eligible studies whereas the remaining 19 were performed at single centers. The control of matched patients were also analyzed in seven studies which were from a healthcare system (*n* = 3)[20,22,24]; healthy community population (*n* = 3)[21,26,27]; or were not defined (*n* = 1)[28].

Population characteristics

The qualitative review of 21 studies included 20155 CP patients and 2007278 control patients (from seven controlled studies). The patients with CP were identified based on the combination of clinical, radiologic, endoscopic and/or histologic findings in 17 studies[17-19,21-23,25,27-36], and diagnosed through ICD-9/10 codes in four studies[20,24,26,37] (Table 1).

Prevalence of bone disease

We performed meta-analysis of 21 eligible studies which included 20155 CP patients evaluated for bone disease.

Prevalence of osteopenia in CP patients: In adult CP patients, the pooled prevalence of osteopenia was 41.2% (95%CI: 35.2%-47.3%, $P < 0.0001$; $\chi^2 = 63.0$, $df = 14$, $P < 0.0001$; $I^2 = 77.8\%$, $\tau^2 = 0.04$)[17-19,23,25,27-32,34-37] (Figure 2A). All of the studies prevalence estimates had high heterogeneity since $I^2 > 75\%$.

Prevalence of osteoporosis among CP patients: The pooled prevalence of osteoporosis in CP patients was 20.9% (95%CI: 14.9%-27.6%; $P < 0.0001$; $\chi^2 = 290.33$, $df = 18$, $P < 0.0001$; $I^2 = 93.8\%$, $\tau^2 = 0.1$)[17-19,21-23,25-37] (Figure 2B). The pooled prevalence of osteoporosis in CP patients had high heterogeneity since $I^2 > 75\%$.

Prevalence of fragility fracture among CP patients: The pooled prevalence of fragility fracture was 5.9% (95%CI: 3.9%-8.4%, $P < 0.0001$; $\chi^2 = 186.0$, $df = 8$, $P < 0.0001$; $I^2 = 95.7\%$, $\tau^2 = 0.02$)[19-21,24,26,32,34,35,37] (Figure 2C). All of the studies prevalence estimates had high heterogeneity since $I^2 > 75\%$.

Factors impacting bone disease in CP patients: Various covariates underwent qualitative assessment for their association with CP related bone disease (Table 3).

Baseline patient characteristics: Female population was excluded in three studies[17,22,28] whereas 6376 (31.6%) female subjects were incorporated in the remaining 18 studies. In addition, three studies excluded post-menopausal females[19,25,33]. The race of CP patients was described in only five studies[20,24,33-35]. Its association with bone disease was investigated only by Hart and colleagues and they observed significantly higher burden among Caucasian population[35].

CP activity: The impact of CP severity on the bone outcomes was investigated in only one third of the eligible studies[17,19,27,28,31,32,35]. These studies observed no correlation with CP severity and alteration in bone mineral density. Moreover, the association of bone disease with duration of CP was also studied and lacked statistically significance[18,29,32,33,35,36]. The studies by Sikkens *et al*[25], and Kuhlman *et al*[30], observed a significant association of bone disease with exocrine insufficiency. Improved bone disease outcomes were observed in patients receiving PERT based on four large sized studies[26,30,35,37]. PERT usage and CP-related bone disease lacked statistical significance in five observational studies[17,22,23,28,32].

Inflammatory factors: Inflammation-based biomarkers such as C-reactive protein and interleukin (IL)-6 levels also yielded non-significant results in the investigation by two groups[27,32].

Endocrine factors: Among the eligible studies, hormones which regulate calcium metabolism have been widely studied. Serum 25-OH cholecalciferol had a positive correlation with bone density in three studies[21,27,30], whereas the remaining reported no significant associations[17,18,22,28,29,32]. Similarly, alkaline phosphatase and calcium had non-significant correlation with bone mineral density in two studies[17,28]. Serum PTH level did not correlate with bone disease in three studies[17,18,28], in contrast to the significant association found by Stigliano *et al*[32], Duggan *et al*[27], and Tang *et al*[36]. Novel bone turnover-based biomarkers *i.e.*, carboxy-terminal telopeptide of type I collagen,

osteocalcin, procollagen 1 amino-terminal propeptide also had non-significant results in limited observational studies[27,36]. Thyroid-stimulating hormones and Insulin-like growth factors 1 were considered by Munigala *et al*[24], but no correlation was found with bone mineral density (BMD). Although hypogonadism was higher in subjects with low BMD in the study by Gupta e*t al*[33], no statistically significant difference was found. Exogenous hormone uses or replacement therapy was not investigated in any of the included studies.

Nutritional factors: The evidence linking BMI with bone disease outcomes has been conflicting. Whereas six studies described higher BMI as a protective factor[19,21-23,30,32,36], others reported an increased risk or non-significant findings[17,31,33,35]. Serum albumin was also explored in two studies with no mention of outcome association[17,21]. Min and colleagues studied the Malnutrition Universal Screening Tool, a validated nutritional assessment tool and observed that a score of 1 or more had significant association with osteopenia and osteoporosis ($P = 0.004$)[31]. Three studies described calcium supplement intake but did not study its relationship with bone disease[21,22,30].

Lifestyle factors: The definitions for exposure to alcohol and/or smoking were heterogeneous with limited evidence on their impact on bone outcomes[17,19,21,23-28,30,32-37]. Outdoor activity and sunlight exposure was only investigated by Joshi *et al*[21], and although correlated positively with vitamin D levels, their impact on osteoporosis was not studied.

Meta-regression
Meta-regression revealed significant association of PERT use with prevalence of osteoporosis [coefficient: 1.7 (95%CI: 0.6-2.8); $P < 0.0001$] but not with osteopenia or fragility fractures. No associations with mean age, sex distribution, BMI, alcohol or smoking exposure, vitamin D deficiency, PTH levels, and diabetes with prevalence of osteopenia, osteoporosis or fragility fractures (Table 4).

Sensitivity analysis

Sensitivity analysis through forest plot calculation was performed using the "remove one study" method as described above. Confidence intervals and heterogeneity was measured through I^2 and no significant alterations were observed after removal of one particular study (Supplementary Table 4).

Study quality and publication bias assessment

All the observational studies were assessed for quality in selection, comparability, and outcome/exposure domain and their scores ranged from 5-8 and were in good agreement (93% agreement, Cohen's κ = 0.87) (Supplementary Table 5). The comparability domain was variable based upon the presence or absence of controls. Visual inspection of funnel plot and Egger's regression for studies describing osteopenia (P = 0.003), and osteoporosis (P < 0.001) demonstrated significant publication bias (Figure 3).

DISCUSSION

Through this systematic review we present the burden of osteopenia, osteoporosis, and fragility fractures in CP patients. The majority of the studies used bone mineral density to quantitate bone disease, which is a validated tool for use in the general population[38]. Our meta-analyses revealed osteopenia and osteoporosis to be prevalent in 41.2% and 20.9% of the CP population, respectively. We also observed a fracture risk of 5.9% among CP patients, which includes low trauma fractures predominantly in the hip, vertebrae and distal radius. These may cause pain, falls, and hospitalizations which may significantly impair the lives of CP patients along with pre-existing morbidities like malabsorption and chronic abdominal pain[39].

Although dedicated studies among CP patients are lacking, reduced bone mass and resultant fractures cause significant pain, reduced functionality, and quality of life in both men and women[40]. Chronic inflammatory conditions affecting the gastrointestinal tract, such as inflammatory bowel disease, celiac disease and chronic liver disease have been

known to disrupt the balance between bone resorption and formation and cause bone disease. Histomorphometric analysis among alcohol related CP patients has revealed low cortical and trabecular bone thickness and endocortical apposition and growth rate as compared to controls[41]. Similarly, increased bone turnover and mineralization defects due to malnutrition have been observed in CP[27,42]. Although recent CP guidelines in the United States and Europe have suggested surveillance of bone-related disorders, studies report poor adherence to these guidelines, suggesting CP-related bone disease is an underappreciated clinical entity[7,8].

CP-related bone disease has been quantified previously by Duggan *et al*[9] in 2014 who observed similar prevalence of osteopenia and osteoporosis *i.e.*, 39.8% and 23.4%, respectively. Since this publication, over the past decade, several additional observational studies have investigated bone mineral density and metabolism in CP patients[24,25,27-31,33-35,37], and therefore, provide a unique opportunity to further investigate the evidence in this clinical domain. Hence, we appraised all the available literature, including the most recent publications, in an effort to contribute evidence for future by also uniquely quantifying fragility fractures which are significant complications of CP-related bone disease.

The current systematic review is powered by high-quality studies with large sample size and clearly defined study population and outcome measures. In addition, strengths of the study include a clearly articulated a priori analysis plan, a thorough search strategy and a conservative analysis. However, our study is limited by variability in the CP definitions from centers worldwide and spanning over 2 decades. Besides inconsistencies in definitions, high heterogeneity in the effect sizes is evident from I^2 mandated performance of metaregression and sensitivity analysis. The heterogeneity was not attributable to any specific study as demonstrated by sensitivity analysis. We observed significant association of osteoporosis with patients with PERT use on metaregression analysis. Although PERT use signifies severe disease, this association doesn't not establish causality and this in conjunction with limited information on the dosage of PERT or nutritional outcomes prevent substantial inferences to be drawn from this

association[43]. We acknowledge significant publication bias, and a priori exclusion of studies in foreign language and conference abstracts[44]. These limitations prevent making categorical recommendations to patients.

Various mechanisms have been hypothesized to cause CP-mediated bone disease. Risk factors for CP such as cigarette smoking and alcohol exposure have been proven to alter the PTH-vitamin D axis and gonadal hormones and cause oxidative stress[41,45-48]. This clinical entity is also hypothesized to be driven by RANK ligand-induced osteoclastogenesis typically stimulated by inflammation-mediated nuclear factor-kappa B ligand[49]. Prior studies have also evaluated the relation of CP with inflammatory markers, such as IL-6, IL-1, and tumor necrosis factor-alpha[50]. Protein malnutrition lowers bone mass whereas deficiency of fat-soluble vitamins contributes to defects in mineralization and thus causes osteoporosis and resultant stress fracture[51,52]. CP is also characterized by low skeletal muscle, weight loss, and low mobility, all of which negatively impacts bone mass[53-55].

CP-related bone disease warrants further investigation to answer a few clinical queries. While CP patients are at risk, the impact of disease severity and duration on bone outcomes are unknown. Additionally, poor correlation between clinical symptomatology, severity and imaging findings in CP patients presents challenges for research[56]. We also systematically assessed various confounders including baseline clinical features and impact of bone turnover and inflammatory markers, albeit our results were unremarkable. The evidence on calcium supplements, hormone levels and outdoor activity among included studies was lacking. The studies that investigated mechanisms of systemic inflammation, bone turn over and malabsorption were underpowered, whereas those pertaining to vitamin D had conflicted evidence[17,18,21,22,27-30,32]. Among this at-risk group, efficacy of preventative therapy for osteoporotic fracture, drug interactions, and adverse effect also remain elusive.

CONCLUSION

In summary, this meta-analysis confirms significant bone disease in patients with CP. We observed significant association of PERT with CP related osteoporosis. Our study calls for improved methodology dedicated at delineation of confounders and studies targeting identification of at-risk CP patients, deeper understanding of mechanisms of CP related bone disease and their implications of treatment response. Fragility fractures are an important consequence of bone disease, which we have found to be increased in patients with CP. Screening strategies in this at-risk population with CP are needed as well as evaluating quality of life due to consequences of bone disease.

ARTICLE HIGHLIGHTS

Research background

Chronic pancreatitis (CP) is a multifactorial fibro-inflammatory syndrome is characterized by nutritional deficiencies, systemic inflammation, and etiological factors like alcohol or smoking may disrupt the balance between bone formation and resorption. These maladaptive alterations may cause osteopenia and osteoporosis, resulting in fragility fractures which result from low energy trauma and have significant implications on quality of life.

Research motivation

Multiple large-sized studies on CP patients including those from multicenter cohorts have investigated the burden of bone disease in CP as well as their association with nutritional, anthropometric, and inflammatory parameters. Thus, with quantitative data on covariates and fragility fractures available, a synthesis of evidence is pertinent.

Research objectives

This systematic review and meta-analysis sought to quantify the prevalence of osteopenia, osteoporosis, and fragility fractures in CP patients and delineate clinical parameters which impact their occurrence.

Research methods

The study included systematic review and then metanalysis of studies describing bone disease in CP patients. A preregistered systematic search enabled identification of original studies from Cochrane Library, Embase, Google Scholar, Ovid Medline, PubMed, Scopus, and Web of Science, from inception until October 2022. The metanalysis was performed using random effect model and the outcomes of interest included prevalence of osteopenia, osteoporosis, and fragility fractures. To assess the association of these outcomes with covariates metaregression using random effect model was performed

Research results

Twenty-one studies were included for systematic review and 18 studies were included for meta-analysis. The pooled prevalence of osteopenia and osteoporosis in CP patients was 41.2% (95%CI: 35.2%-47.3%) and 20.9% (95%CI: 14.9%-27.6%), respectively. The pooled prevalence of fragility fractures described among CP was 5.9% (95%CI: 3.9%-8.4%). Meta-regression showed no associations of bone outcomes in CP patients with mean age, sex distribution, body mass index, alcohol or smoking exposure, diabetes, serum parathyroid levels, and vitamin D deficiency with prevalence of osteopenia, osteoporosis or fragility fractures. A significant association of pancreatic enzyme replacement therapy use with prevalence of osteoporosis [coefficient: 1.7 (95%CI: 0.6-2.8); $P < 0.0001$]. Due to sparse data on systemic inflammation, CP severity, and bone mineralization parameters a formal meta-analysis was not feasible.

Research conclusions

This meta-analysis confirms significant bone disease: osteopenia, osteoporosis, and fragility fractures in CP patients. Although pancreatic enzyme use had significant association with osteoporosis, the link between osteopathy and various patient or study-specific factors remains unclear. Further investigation is needed for delineation of at-risk

population, to understand the mechanisms of CP-related bone disease, and assess the therapeutic response to treatment modalities.

Research perspectives

Our study calls for dedicated studies targeting delineation of confounders and identification of at-risk features in CP patients. There is also a knowledge gap in therapeutic response among CP patients with bone disease.

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