January 8, 2023

Dr. Lian-Sheng Ma,

The Editor, World Journal of Gastroenterology

Ref: Submission ID Manuscript NO: 81472

Dear Dr. Ma,

We sincerely thank the editors and reviewers for their time and expertise in reviewing our manuscript “Burden of Bone Disease in Chronic Pancreatitis: A Systematic Review and Meta-Analysis**”**. We appreciate the opportunity to revise and resubmit the manuscript and have addressed all the reviewers’ comments. We provide a point-by-point response to the comments provided by the two Reviewers, with both a clean and a tracked edited version of the manuscript.

Thank you for your consideration, and we would be happy to address any questions and/or comments by the editorial board and reviewers.

Sincerely,

Sunil Sheth, MD

Reviewer #1: Specific Comments to Authors: authors worked on very attractive topic. The manuscript is well written and i think it would be interesting for the readers.

We appreciate Reviewer 1's comment on our manuscript.

Reviewer #2: Comment#1: This is a good article, which has obvious reference significance for understanding the incidence of bone disease and its influencing factors in patients with chronic pancreatitis.

However, there are many factors that can affect bone diseases, especially osteoporosis, including hormone levels, poor nutrition, outdoor activities, calcium supplements, excessive weight loss, and hormone use. If more factors could be analyzed, it would be even more helpful.

We appreciate Reviewer 2's comment on our manuscript. Per their recommendation, our Result Section has been modified to include dedicated qualitative analysis on

1) Hormone levels and use:

> *<u>Endocrine factors:</u> 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 parathyroid hormone (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., Duggan et al., and Tang et al. (27, 32, 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., but no correlation was found with bone mineral density (BMD). (24) Although hypogonadism was higher in subjects with low BMD in the study by Gupta et al., no statistically significant difference was found. Exogenous hormone use or replacement therapy was not investigated in any of the included studies. (33)*

2) Nutritional parameters- which evaluates relationship of CP-bone disease with BMI and nutritional parameters.

> *<u>Nutritional factors</u>: The evidence linking body mass index (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 (MUST), a validated nutritional assessment tool and observed that a score of 1 or more had significant association with osteopenia and osteoporosis (p=.004) (31). Three studies described calcium supplement intake but did not study its relationship with bone disease(21, 22, 30).

3) Outdoor activities, 4) Calcium supplements, as below:

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., and although correlated positively with vitamin D levels, their impact on osteoporosis was not studied (21).

Included studies lacked data on relationship of bone disease with excessive weight loss, exogenous hormone use, and (outdoor activities) sunlight exposure among CP patients. These limitations have been highlighted in the Discussion section as below:

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.

We also performed metaregression on Vitamin deficiency and serum PTH levels.

Covariates	**Osteopenia#**		**Osteoporosis#**		**Fragility Fracture#**	
Vitamin D Deficiency(%)	-0.0[95%CI: -0.02-0.0012]	P=0.4	-0.002[95%CI: -0.004-0.001]	P=0.2	0.00[95%CI: -0.003-0.005]	0.5
Serum PTH levels	0.002[95%CI: -0.02-0.02]	P=.05	0.0[95%CI: -0.02-0.03]	P=0.4	-*	-*

*insufficient values

Reviewer 2 Comment#2: In addition, it is suggested to discuss the causes and possible mechanisms of bone diseases induced by chronic pancreatitis in the section of discussion.

Based on Reviewer 2's recommendation, we have expanded on the causes and possible mechanisms of bone diseases induced by CP in our Discussion section as below.

Various mechanisms have been hypothesized to cause CP-mediated bone disease. Risk factors of CP like cigarette smoking and alcohol exposure have been proven to alter the PTH-vitamin D axis, 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 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 cause osteoporosis and resultant stress fracture (51, 52). CP is also characterized by low skeletal muscle, weight loss, and low mobility which negatively impacts bone mass (53-55).