May 19, 2017

Ze-Mao Gong
Science Editor
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Dear Mr. Gong:

We thank you and the reviewers for the constructive critique of our manuscript, "Less Common Etiologies of Exocrine Pancreatic Insufficiency," (ESPS Manuscript NO: 30060). We appreciate the feedback from peer review, and have addressed the reviewers' comments and incorporated the recommended revisions.

Revisions to the submission are tracked in the manuscript and are described in detail below. Whenever available, PubMed IDs and DOIs have been added to the reference citations in the bibliography. A new audio recording of the Core Tips, modified, signed Conflict of Interest Statements, and a new, signed Copyright Assignment form have been uploaded. We hope that you will now find our manuscript suitable for publication in *World Journal of Gastroenterology*.

Kind regards,

Vikesh K. Singh, MD, MSc

Division of Gastroenterology

Johns Hopkins University School of Medicine

1830 E Monument Street, Room 436

Baltimore, MD 21287

Email: vsingh1@jhmi.edu

Office phone: +1 410-614-6708

Fax: +1 410-614-7631

Reviewer #1

1. Literature searches: I recommend updating of literature on this field in last year (last update was performed in September 2015).

- Response: The literature search has been extended through December 5, 2016 (p. 7, paragraph 1).

2. Diagnosis of EPI: There are two new diagnostic methods that should be included and discussed in the text: the 13C-mixed triglyceride (C-MTG) breath tests and secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging (sMRCP). Please include changes also in the table 4.

- Response: A brief discussion of the ^{13}C-MTG breath test and sMRCP has been added to the manuscript (p. 10, paragraph 2) and Table 4.

3. Pancreatic enzyme replacement therapy: It will be useful for your readers that you also mention type and doses of PERT recommended for treatment of EPI.

- Response: The reader has been directed to publications on porcine lipase preparations and to publications from national and professional organizations for recommended dosages, including those recommended by the reviewer (p. 11, paragraph 1).

4. Diabetes mellitus and EPI: The authors reviewed literature with high prevalence of EPI in patients with DM type 1 and type 2 (up to 57%). Those studies were performed with different diagnostic methods. Considering the variations and limitations of tests, test selection has undoubtedly contributed to the variations in the EPI prevalence results. Another likely cause of this variation is the underestimation of type 3c DM (chronic pancreatitis was not excluded with radiologic or endoscopic procedures in those studies). Some data has shown that nearly half of T3cDM patients are misdiagnosed as type 1 or type 2 DM. That can be explanation for rather high prevalence of EPI in DM type 2.

- Response: The reviewer's point is well taken. A caveat has been added at the end of the paragraph leading into discussion of diabetes and EPI (p. 14, paragraph 2).

5. Gastrointestinal surgery and EPI: Maybe you can discuss also bariatric gastric by-pass surgery in overweight patients?

- Response: A brief discussion of bariatric bypass surgery has been added on p. 25, paragraph 3).

6. Table 1: The authors mentioned hemochromatosis as a definite association with EPI. Do you have some citations on that topic? To reviewer's best knowledge there are no studies on EPI in hemochromatosis (I searched Medline). If they are, please put them in the reference list.

- Response: As noted in the manuscript text (p. 17, paragraph 3), both Cui et al (*Pancreatology* 2011; **11:** 279-294) and Ewald et al (*Diabetes Metab Res Rev* 2012; **28:** 338-342) have reported that hemochromatosis may be associated with type 3c diabetes. Per diagnostic criteria, all patients with type 3c diabetes display signs of EPI. We have now also cited those 2 references where Table 1 is called out.

7. I think that diabetes is not extrapancreatic condition. [Comment on Table 1]

- Response: The terms "pancreatic disease" and "extrapancreatic conditions" have been removed from Table 1.

8. Aging and EPI? That was not discussed in the text. [Comment on Table 1]

- Response: A brief section on aging and EPI has been added to the text (p. 19, paragraph 2).

Reviewer #2

1. Discussion should be corrected to Methods on page 7.

- Response: "Discussion" has been changed to "Methods" on p. 7.

2. Table 1: I would omit pancreatic duct obstruction, since it is caused by pancreatic tumor or chronic pancreatitis, which are already in the table. Type 3c diabetes is not an extrapancreatic disease, but pancreatic.

- Response:
    - "Pancreatic duct obstruction" has been removed from Table 1.
    - The terms "pancreatic disease" and "extrapancreatic conditions" have been removed from Table 1.

3. Page 9: I do not consider fecal elastase test an indirect test, because it measures directly the quantity of a pancreatic enzyme. Indirect tests measure exocrine pancreatic function indirectly by assessing the secondary effects resulting from a lack of digestive enzymes (eg PABA, pancreolauryl test, fecal fat etc).

- Response: Direct tests are usually defined as those that measure pancreatic secretions at their source, due to stimulation, not in the feces sometime after release from the pancreas. By this definition, fecal elastase is an indirect test.

4. Abbreviations should be used consequently throughout the manuscript (e.g. PERT).

- Response: Abbreviations have been used consistently except when starting a sentence or paragraph.

5. Page 15: Type 3c diabetes, is recognized as a distinct category of diabetes by WHO.

- Response: The reviewer is correct that the 1999 WHO guidelines recognize that diabetes may be caused by various other conditions (eg, pancreatitis, cystic fibrosis), although we do not find the specific term "type 3c" in the guidelines. Nonetheless, that section of the manuscript text has been deleted (p. 14, paragraph 2).