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Dear Editors:

Respectfully submitted to *WJGP* is *revision* of our manuscript, "Energetic Etiologies of Acute Pancreatitis?" We have replied to each and every point below, our *responses in bold, italic face, and underlined*, following the verbatim reviewer comments in quotation marks:

REVIEWER COMMENTS:

REVIEWER 00724362

1. "This is a very interesting manuscript from the clinical point of view. Both hypothesis are interesting. Etiology of TENS is probably similar with ESWL induced pancreatitis. I wonder if authors have some experiences with "fat burners" and pancreatitis too?."

RESPONSE: We thank the reviewer for his or her interest in our manuscript. We admire the speculation that putatively TENS-related pancreatitis may be similar to ESWL-induced pancreatitis, although we wonder if perhaps the mechanical trauma associated with sound waves in ESWL wouldn't be quite different than the neurogenic trauma that we propose. We have not noticed any cases temporally associated with "fat burners"

REVIEWER 02548034

1. "The authors stated that the proportion of idiopathic acute pancreatitis is increasing, and cited two articles that are however either irrelevant or unsupportive. With the advent of new or aggressive diagnostic approach to acute pancreatitis, the proportion of unknown etiology should be decreasing. (references: Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic

and recurrent pancreatitis, what should be done? World J Gastroenterol. 2008;14(7):1007-10. Thevenot A, Bournet B, Otal P, Canevet G, Moreau J, Buscail L. Endoscopic ultrasound and magnetic resonance cholangiopancreatography in patients with idiopathic acute pancreatitis. Dig Dis Sci. 2013;58(8):2361-8.)"

RESPONSE: We respectfully point out that the two references we cited (#2, and #3) do in fact relevantly support our statement that the idiopathic etiology is increasing: Joergensen et al state clearly on page 2992, in the first line of the second paragraph, in the section Etiology, that "Idiopathic pancreatitis was significantly more common after 1999 than before." Perhaps this reviewer read only the abstract, which is worded in a slightly misleading manner such that one might think at first glance that Joergensen et al are reporting that the increased cases of idiopathic pancreatitis are explained by genetic mutations and are not therefore idiopathic. However, this is incorrect, and a reading of the body of the paper clearly shows that this paper finds an increase in idiopathic pancreatitis over time. Similarly, on page 23 in Table 4 of our other reference, Lankische et al, there is clear support for our statements both that, "the etiology of the vast majority of cases is identified as either alcohol or biliary stones" and that the idiopathic proportion is increasing (Table 10 in Lankische shows a 10% increase [NS]). Again, if the reviewer read only the abstract, then it would be understandable that the information in Table 4 could be missed. The two references cited by the reviewer do not address any epidemiologic increase or decrease, but they do address the point raised by the reviewer, viz, that more aggressive testing can convert "idiopathic" cases to known-cause cases, a point we never contradict. Could it not be the case that the well recognized increase in all-cause pancreatitis outstrips the increase in conversion of idiopathic to known-cause pancreatitis, such that the number of unknown cases is increasing, along with all other cases? Nevertheless, we have added text to address the reviewer's points.

2. "Two cases in the report have history of "suspected biliary pancreatitis" and "a remote history of alcoholic pancreatitis". I wonder if these two cases can be categorized as idiopathic although the risk of recurrence is reduced after cholecystectomy and abstinence of alcohol. (references: Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. N Engl J Med. 1992;326(9):589-93. Nordback I, Pelli H, Lappalainen-Lehto R, J?rvinen S, R?ty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009 Mar;136(3):848-55.)"

RESPONSE: We agree that conversion of alcoholic pancreatitis to autonomous pancreatitis is common and that relapses of pancreatitis can happen even in the absence of further alcohol. Indeed, we see this frequently in our busy pancreatic surgery practice. We therefore were careful add to Table 1 that this patient (patient #4) had alcohol as the inciting etiology. To further emphasize this good point that the reviewer makes, we have added additional text to the discussion to

highlight the possible coincidence in patient #4 between exacerbations of autonomous alcoholic pancreatitis and the consumption of energy drinks.

3. "The second case appears to have mild acute pancreatitis associated with an implanted electrical nerve stimulator device for chronic back pain due to a fall. However, it is hard to say "idiopathic" without further examinations to exclude "occult causes" of pancreatitis. (see references in comment 1)"

RESPONSE: We appreciate this comment, and have added text to Table 1 to make clear that missed sludge or medications could also, of course, explain the pancreatitis in patient #2.

4. "The third case has severe acute pancreatitis associated with a TENS device for back pain during a 10-hour car trip. She received necrosectomy for severe, extensive, necrotizing pancreatitis and disconnected-duct syndrome. How the TENS was used by the patient is not reported. The pathology as well as other exams for possible cause of the attack is also not reported. A temporal association is not sufficient for causality although the proposed neurogenic mechanism is interesting.."

RESPONSE: We have added the details that the reviewer requests. We appreciate that the reviewer agrees with us that the proposed neurogenic mechanism of TENS-associated pancreatitis is interesting. Therefore, we are motivated to offer Figure 1 in the hope of better and more clearly presenting the very interesting proposed mechanism.

REVIEWER 03014597

1. "Interesting and thorny topic related to the study of new etiologies in acute pancreatitis. The onset of acute pancreatitis in temporal relation to the use of TENS and energy drinks assumption is documented in sporadic cases reported by the author. Could be useful in the future to assess further cases in a multicenter setting, trying to clear more confounding factors. Only such minor questions: -anatomical and infective possible causes were routinely ruled out? -combined alcol + energy drink assumption was clearly certified?."

RESPONSE: We thank the reviewer for these comments. We agree that future studies are in order, and we have stressed this in the Conclusions. Regarding other etiologies, please refer to the response to reviewer 02548034. Regarding the combination of alcohol and energy drinks, we do not know of any cases where consumption of alcohol combined with energy drink occurred. Regarding the interesting and thorny nature of this topic, we could not agree more, and offer Figure 1 in the hope of better and more clearly presenting the very interesting proposed mechanism.

ADDITIONAL CHANGES AND NOTES

1. "Authorship"

NOTE: We have corrected an error in the byline, viz, that Dr. Shmelev should be first shared author with Dr. Abdo. Apologies for any confusion this may cause.

2. "Required documentation"

NOTE: We are happy to add the required documentation after consultation with the editors, since it is not clear which of the list applies to us, since some items clearly do not, such as "7 17849-Biostatistics statement," given that our MS contains no statistics.

I can verify that this manuscript is original work, that it has not been published previously, and that it has been reviewed and approved by all authors, none of whom have any conflict of interest, and all of whom deserve authorship.

Please do not hesitate to contact me by phone, fax, or e-mail as per below regarding any issues. Your attention to our manuscript submission is greatly appreciated. I remain

Sincerely yours,



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