

ANSWERING REVIEWERS



February the 4th, 2014

Dear Editors,

Please find enclosed the edited manuscript in Word format (file name: ESPS_Ms_No.5701-Gasparetto-2nd Rev).

Title: Crohn's disease and growth deficiency in children and adolescents

Authors: Marco Gasparetto MD, and Graziella Guariso Prof

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5701

1. Replies to Reviewer 00035982

Dear Reviewer,

Thank you for your suggestions, which have helped us to improve the quality of our manuscript.

Below are point-by-point answers to your observations:

1. As suggested, the manuscript has been thoroughly revised to make it more readable, with the support of an English mother-tongue professional scientific translator.
2. We have amended the "aim" of the Abstract as follows: "This narrative review highlights the most current evidence on growth deficiency in children and adolescents with CD, aiming to provide advice on how to assess and manage nutritional concerns in these patients".
3. The search terms we mention in the Abstract are actually the ones we first used for our Medline Research and collection of papers to review. We subsequently had access to a wide range of additional papers on the same topic identified by the electronic systems as being connected to those detected in our first selection process. Once we had collected all the papers on our topic, we made our selection (year of publication 2008-2013, type of study performed). As suggested, we have added the terms "weight, height, growth, weight loss" to the key words of our manuscript to provide potential readers with a less restrictive access.
4. The Results and Conclusions sections of the Abstract have been rearranged, as suggested. The paragraph "In pediatric CD patients, a prolonged diagnostic delay, a high initial activity index, and a stricturing/penetrating type of behavior may cause growth deficiencies (in weight and height) and delay puberty" has been moved from the Conclusions to the Results. The Conclusions now focus on the role of a targeted intense initial (top down treatment) for patients with nutrition and growth impairment. The pivotal role of enteral nutrition is also mentioned at this point.
5. Grammar and sentence construction have been checked and improved by an English mother-tongue translator.

6. As requested, the sentence on page 4 has been amended as follows to emphasize that the Paris classification is specific for children: "Assessing growth in IBD patients of developmental age is so important that it was included among the key points in the Paris classification of pediatric CD, which replaced the previous Montreal classification [24]".
7. Concerning changes in bone turnover, we meant to say that both bone formation and reabsorption are impaired in children with IBD, so the whole process of bone remodeling is ultimately affected. The two normal processes underlying bone health (reabsorption and formation) become slower, giving rise to a weaker bone tissue with a slower rate of maturation, finally reflected in poor growth. The first paragraph on page 5 has been rewritten as follows to clarify the concept: "Bone formation and reabsorption are significantly involved in bone health and growth. In children with CD, both of these processes are impaired so bone growth is ultimately suboptimal [49]".
8. We agree, and have now added the following reference: [71] Whitten KE, Leach ST, Bohane TD, Woodhead HJ, Day AS. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 2010; 45(4): 399-405. [PMID:19957194 DOI: 10.1007/s00535-009-0165-0]. We have commented on these findings as follows (beginning of page 8):

"A very interesting report from Whitten KE et al. [63] supports the role of enteral nutrition in improving bone metabolism. The Authors enrolled 23 children with newly-diagnosed CD and 20 controls. Children with CD were treated for 8 weeks with EEN, and inflammatory markers, nutritional markers (height, weight), and bone markers (C-terminal telopeptides of Type-1 collagen [CTX] and bone-specific alkaline phosphatase [BAP]) were measured before and after the treatment. At diagnosis, children with CD had higher serum CTX than controls ($P = 0.0003$). After the period of EEN, their CTX levels fell significantly ($P = 0.002$), and their serum BAP levels ($P = 0.07$) increased significantly ($P = 0.02$), both normalizing to control levels. This evidence indicates that, as well as reducing inflammation, decreasing disease activity, and improving nutrition in children with newly-diagnosed CD, EEN therapy also normalizes serum markers of bone turnover, suggesting an improvement in bone health [63]".
9. The names of bacterial organisms are now provided in the correct/standard format i.e. *Helicobacter* (H.) *hepaticus*, on page 5.
10. To improve the readability of the paper and better connect the various parts, the order of the sections has been rearranged as follows:
 1. Introduction
 2. Growth issues in pediatric Crohn's disease
 3. Nutritional concerns in pediatric Crohn's disease
 4. Bone health and pediatric Crohn's disease
 5. Puberty-related issues in pediatric Crohn's disease
 6. Management of growth and pubertal issues in pediatric Crohn's disease
 7. Conclusions
11. The three tables have been shortened and simplified to provide readers with a more useful and

immediate tool.

Thank you again for considering our manuscript for *World Journal of Gastroenterology*.

Sincerely yours,

Marco Gasparetto, MD

A handwritten signature in dark ink, appearing to read 'Marco Gasparetto', with a stylized, cursive script.

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