Author's response to reviews

Title: Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease

Authors:

Mostafa A El-Hodhod (moshodhod@yahoo.com)
Ahmad M Hamdy (a_hamdy13@hotmail.com)
Amal A Abbas (drhazemfawzy@hotmail.com)
Sherine G Moftah (sherinemoftah@yahoo.com)
Alhag A Ramadan (alhagramadan@yahoo.com)

Version: 2 Date: 9 April 2012

Author's response to reviews: see over
Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease

Dear Editor of BMC Gastroenterology

Thank you for the great effort in revising this manuscript and for the valuable comments of the eminent reviewers. Here is a list of comments and their responses in a point-to-point way. The manuscript was uploaded as 2 copies; one with the changes being highlighted and one without the highlighting.

I hope our responses are to the required standard of your prestigious journal

Many thanks

Mostafa El-Hodhod

moshodhod@yahoo.com
**Editorial Requirements:**

1- Structure: Please check the instructions for authors on the journal website to ensure that your manuscript follows the correct structure for this journal and article type.

**Response:** It was revised and corrected.

2- kindly change "Introduction" Section into "Background" :

**Response:** It was done

3- Conclusions: < must be placed at the right section > :

**Response:** It was done

4- Competing interests: < must be placed at the right section > :

**Response:** It was done

5-Tables:

**Response:** all problems fixed.

6-Authors’ information: Please place the Authors' Contributions section after Competing interests. Please check the instructions for authors on the journal website for the correct format to use for Authors' Contributions.

**Response:** It was done

7- Acknowledgements:

**Response:** It was done
Reviewer 1

1- The introduction session is probably too brief; at least few more information about the exact role of FGF23 and PHEX should be better clarified, so that the hypothesis would sound more interesting and intriguing.
Response: this was considered and more information was given about role of FGF23 and PHEX in the background section lines 63 – 74

[Fibroblast growth factor 23 (FGF23) belongs to the group of phosphatonin, which enhance renal phosphate excretion and inhibit renal 25-hydroxy-vitamin D3 1α hydroxylase (10). Increased FGF 23 secretion was proved to be the mechanism of bone disease in many diseases including tumor induced osteomalacia (11) and X linked hypophosphatemic rickets (12). Decreased degradation of FGF23 was found to be the mechanism of bone disease in autosomal dominant hypophosphatemic rickets (13). Impaired renal excretion of FGF23 was proved to be the mechanism of renal osteodystrophy and post-transplant hypophosphatemia (14).

The PHEX (phosphate-regulating with homologies to endopeptidases on the X chromosome) gene encodes a Zinc-metalloendopeptidase expressed primarily in osteoblasts and odontoblasts. Studies seemed to confirm the hypothesis of proteolytic degradation of FGF-23 by PHEX (15). The down-regulation of the PHEX gene results in decreased degradation of FGF-23 and a subsequent increase in its circulating levels (16).]

2- Which therapy enrolled patients were following before and after the flare;
Response: This was made clear in the methods section lines 133 – 138

[Treatment: For induction of remission, all patients received oral prednisone (1-2 mg/kg/day) for 3-4 weeks. Parenteral antibiotics and other supportive measures were individually adjusted. After induction of remission, patients were then maintained on 5 amino salicylic acid (35). Six CD patients subsequently received infliximab as add-on therapy (36).]
One patient with UC underwent total proctocolectomy with ileo-anal anastomosis (37).

3- Time for the second evaluation after reaching the remission (weeks, months??)
Response: This was made clear in subjects and methods section lines 90 – 93

[Patients underwent clinical and laboratory reassessment 3 months after achieving remission depending on feasibility of follow up visits and availability of required tests as DXA scan. The duration between the initial evaluation "flare" and reassessment "remission" ranged between 4 and 9 months (mean of 7.12 +/- 2.8 months).]

4- Into the discussion session it should be stated issues related to bone density and time related to normalization/reduction
Response: This was considered in discussion section lines 227 – 232

[This degree of improvement was achieved in a period of 7.12 +/- 2.8 months between the flare and remission assessment. Improvement of BMD in such a relatively short period is consistent with Viapiana et al., (43) who found that a 3 months period of intensive nutritional therapy in anorexia nervosa was sufficient to show the significant improvement in BMD. Similarly, Bhambri et al., (44) found that BMD measured by DXA was significantly improved but not to base line after therapy for 2.8+/-1.4 months.]

5- Clarify, in case of vit D deficiency whether a therapeutical intervention was provided and if not (as it appears reading this article), why and how this can be justified
Response: Calcium and vitamin D supplementation were instituted to all IBD patients after enrollment in flare and the following was added to the subjects and methods section lines 140 – 142

[Nutritional support after enrollment in the flare state included calcium (500 – 1000 mg daily) and oral vitamin D₃ supplementation as 1000 IU daily for non-deficient and 10000 IU daily for deficient children.]
Reviewer 2

A- Major Compulsory Revisions

In the DISCUSSION:

a- Could you please explain more extensively the importance of unraveling the defects in bone metabolism in IBD patients, especially children, and are you then able to hypothesize a clinical implication deriving from your findings?

Response: This was considered and added to discussion lines 304 – 311

Controversy exists about the relation between decreased BMD and fracture risk among children with IBD (53). However, low BMD during childhood is associated with increased fracture risk later in adult life (54). Bone metabolism in children is characterized by predominant bone modeling with simultaneous activity of both osteoblasts and osteoclasts on different parts of the bone. Therefore, the principles of bone loss observed in adult patients with chronic inflammation are not directly applicable to children (55). Understanding the specific underlying mechanisms for decreased BMD among children with IBD may help to implement more effective therapies for this complication.

b- Another important variable when assessing improvements in bone metabolism is evaluation of physical activity, do you have the chance to evaluate this variable when assessing the BMD improvements in your children?

Response: Unfortunately, we did not include a scale to measure degree of the physical activity. But we can say that patients, prior to flare, were not bed ridden but were ambulant and most of them were attending their full-day school activities. The hospital admission ranged between 3-4 weeks. The remaining time till reassessment was spent with their normal range of activity with the exception of strenuous exercises. This was added to the manuscript in the methods section lines 143 - 148.
c- In the discussion there is a sentence that, to me, appears not too clear as its reference number 39 doesn't appear correlated to the sentence, could you please check and explain?
Response: We meant that we used serum level of 25 (OH) vitamin D$_3$ as a measure of vitamin D status. This was rephrased in manuscript line 237 and the reference was changed.

d- Did you note any difference in the flare values of BMD, FGF 23 and the other biochemical markers, in patients with a new diagnosis compared to patients with a previous diagnosis (and so with a past history of therapy!)?
Response: Because the number of new cases (1st diagnosis) was little, we were not able to have a sound comparison between new and old cases regarding the different parameters. However, the regression analysis did not show significant impact of duration of the disease on the BMD. This finding might indirectly cover the raised concern

B- Minor essential revisions

a. In the PTH paragraph, in the first sentence "high" should be changed in "higher".
Response: This was fixed in the manuscript (line 274).