Format for ANSWERING REVIEWERS

August 28, 2014

Dear Editors,

Please find enclosed the edited manuscript in Word format (file name: Hyperoxaluria revised manuscript)

Title: Primary and Secondary Hyperoxaluria: Understanding the enigma

Author: Bhavna Bhasin, **Hatice Melda Ürekli**, Mohamed G Atta

ESPS Manuscript NO: 12744

Dear Editors:

We would like to thank you and all the reviewers for their valuable comments on this review paper. We revised our manuscript according to the thoughtful input from the peer-review process. We have provided a point-by-point response to the reviewers' comments below and highlighted the changes in the manuscript. We have hope that you will view our revised manuscript favorably.

Sincerely,

Bhavna Bhasin, MD

Reviewer #1:1. Quite a long and detailed review on the subject. It should be shortened for readers' attention.

Response: We believe that the manuscript is designed to be a comprehensive review and should not be shortened since it can be used as a reference for the interested reader.

Reviewer #2: In this manuscript, the authors reviewed the primary and secondary hyperoxaluria with the literature available to date. However, I have the following comments which need to be addressed before publication.

1. **Abstract: "Definitive diagnosis of primary hyperoxaluria is achieved by genetic studies and liver biopsy, if genetic studies are inconclusive."- this statement is not clear**

   Response: We have revised this statement which now appears as:

   "Definitive diagnosis of primary hyperoxaluria is achieved by genetic studies and if genetic studies prove inconclusive, liver biopsy is undertaken to establish diagnosis."

2. **Abstract: "We also have limited knowledge of role of transplantation in secondary hyperoxaluria"- This statement is unrelated and needs to be removed**

   Response: We have deleted this statement from the abstract.

3. **Page 8: This form of hyperoxaluria is seen in partial gastrectomy, bariatric surgery, jejunoileal bypass, and inflammatory bowel disease. – give a reference for this statement.**

   Response: We have added the appropriate references

4. **Page 12-13: "**In PH patients with ESRD, plasma oxalate levels is typically higher than 80 µmol/L while in non PH hyperoxaluric patients, the plasma oxalate level may range between 30-80 µmol/L." Along with this statement, the authors are requested to include the plasma oxalate levels for normal non stone forming subjects.

   Response: We have added the plasma oxalate levels in normal subjects and this line now reads as:

   "This is in contrast to plasma oxalate levels of 1-5 µmol/L in normal subjects."

5. **1.73 m^2 was used throughout the manuscript. Please describe how you will arrive at 1.73 m^2 and also state the reference. This will help readers to understand without going back to reference.**

Response: We have added an additional statement and reference to explain this on page 12, para 2, line 1. This line now reads as:

"The initial biochemical tests include urinary oxalate excretion preferably measured in 24 hour urine collection and adjustment of the oxalate excretion per 1.73 m^2 of the body surface area is recommended."

Reviewer #3: 1. In abstract section on diagnostic tools, I recommend to exclude the PCR test to detect Oxalobacter formigenes in the stool. Since the diagnostic accuracy of this test has not been generally substantiated

Response: We have deleted this line from the abstract.

2. In the treatment measure authors should further elaborate as to why the intestinal absorption of oxalate is limited in patients with PH.

Response: We have added an explanation for this effect along with the appropriate reference and this line now reads as:

"In a study by Sikora et al, intestinal absorption of oxalate in patients with PH was noted to be less than 7%. This was attributed to less absorption and translocation of the SLC26A6 transporters favoring oxalate secretion over absorption(78)."

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