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November 19, 2015

Dr. Shui Qiu
Science Editor, Editorial Office
Baishideng Publishing Group Inc.

Dear Dr. Qiu:

World Journal of Hepatology #22919.

Thank you for your careful review of manuscript #22919 entitled, "Portal hypertensive gastropathy: A systematic review of the pathophysiology, clinical presentation, natural history, and therapy" by Mihajlo Gjeorgievski and Mitchell S. Cappell submitted as a solicited systematic review to World Journal of Hepatology. The manuscript has been thoroughly revised as per the criticisms of the reviewers as follows.

Reviewed by 00182548

Criticisms: This review is very good documented. The authors analyzed numerous clinical, endoscopic and biological data. They offer a complete picture of current knowledge on portal hypertensive gastropathy. 1. I suggest to authors to make a separate chapter on the pathophysiology of the disease, even if it is not completely understood. 2. There are some spelling mistakes that should be corrected.

Authors' responses to criticisms:

1. Although this systematic review is somewhat lengthy with numerous tables and many references, the authors believe that the journal editors would prefer that this review be published as one article rather than two. We have therefore maintained the manuscript as one paper. However, should the editors want us to split the manuscript into two, we would gladly accommodate this request.

2. Many spelling mistakes and typos have been corrected throughout the manuscript, especially in the citations of references.

Reviewed by 00742516

Kim et al. (20,)

3. Page 6, line 20 - patient age, patient sex, ... change it to 'patient age, sex, ...

Response:

CHANGED TO:

patient age, sex, or cirrhosis etiology

FROM:

patient age, patient sex, or cirrhosis etiology

4. Page 8, last paragraph - This paragraph describes etiology of liver diseases rather than duration of liver diseases. It should either be deleted or moved to other section.

Response

CHANGED TO:

Page 8, last paragraph is moved to section entitled **3. Cirrhosis etiology** from section entitled **4. Liver disease duration**

5. Page 9, line 9 - (odds ratio (OR)=2.68...)

Response:

CHANGED TO:

(odds ratio (OR)=2.68; 95%-CI: 1.16–6.20, $p=0.021$)

FROM:

(OR=2.68; 95%-CI: 1.16–6.20, $p=0.021$)

6. Page 9, line 20 - change 'odds ratio=0.53' to 'OR=0.53'

Response

CHANGED TO:

logistic regression model (OR=0.53, 95%-CI:

FROM:

logistic regression model (odds ratio=0.53, 95%-ORCI:

7. Page 11, line 16 - change 'portal diameter' to 'portal vein diameter'

Response

CHANGED TO:

They found that the portal vein diameter in cirrhotic patients

FROM:

They found that the portal diameter in cirrhotic patients

8. Page 12, line 8 - 64 represents for 74%. Shouldn't the number 22 be changed to 24 to represent the rest of 26%?

Response

CHANGED TO:

In the study by Sarin et al.^[16], 86 (9%) of 967 patients with prior variceal bleeding treated with endoscopic sclerotherapy, had PHG at EGD of whom 22 (26%) had PHG before variceal eradication and 64 (74%) developed PHG after variceal eradication.

FROM:

In the study by Sarin et al. (16), 88 (9.1%) of 967 patients with prior variceal bleeding treated with endoscopic sclerotherapy, had PHG at EGD of whom 22 (26%) had PHG before variceal eradication and 64 (74%) developed PHG after variceal eradication.

9. Page 12, line 24 - change 'but some studies ...' to 'but some studies ...'

Response

CHANGED TO:

but some studies showed worse

FROM:

but other studies showed worse

10. Page 13, line 23 - change '95% ORCI' to '95% CI' Please consult a statistician. I have not seen people using 95% ORCI before.

Response

CHANGED TO:

OR=0.99, 95%-CI: 0.99-0.998;

FROM:

OR=0.99, 95%-ORCI: 0.99-0.998;

11. Page 14, line 4 - add 'PATHOGENESIS' in bold font before 'Hemodynamic changes'. 'Hemodynamic changes' should be bold too.

Response

CHANGED TO:

PATHOGENESIS

Hemodynamic changes

FROM:

Hemodynamic changes

12. Page 15, line 10 - (93, 94, 95, 96, 97), to (93, 94, 95, 96, 97)

Response

CHANGED TO:

in humans with PHG^[93-97],

FROM:

In humans with PHG (93, 94, 95, 96, 97)

13. Page 15 - change 'MOLECULAR MECHANISMS' to 'Molecular Mechanisms'

Response

CHANGED TO:

Molecular Mechanisms

FROM:

MOLECULAR MECHANISMS

14. Page 17, line 11 - be consistent with the format for '6-keto-PGF1a' (see page 20)

Response

CHANGED TO:

6-keto-PGF_{1α},

FROM:
6-keto-PGF_{1-α},

15. Page 18, line 23 - 'HPG' to 'PHG'

Response

CHANGED TO:

and hyperdynamic circulation in PHG

FROM:

and hyperdynamic circulation in HPG

16. Page 19, line 2 - 'controls' to 'controls.'

Response

CHANGED TO:

healthy controls.

FROM:

healthy controls

17. Page 19, line 18 - 'prostaglandin E2' to 'PGE2'

Response

CHANGED TO:

a PGE2 analogue,

FROM:

a prostaglandin E2 analogue,

18. Page 20, line 17 - as mentioned prior be consistent with the format for '6-keto-PGF_{1-α}'

Response

CHANGED THROUGHOUT TO:

6-keto-PGF_{1α},

19. Page 20, line 21 - suggest rephrasing the sentence to 'in the serum and in the mucosa of the gastric fundus of cirrhotic patients with PHG'.

Response

CHANGED TO:

Ohta et al.^[121] found significantly elevated serum levels of 6-keto-PGF_{1α}, a metabolite of prostacyclin, in cirrhotic patients with PHG. They also reported that these patients had significantly elevated levels of 6-keto-PGF_{1α} in the mucosa of the gastric fundus.

FROM:

Ohta et al.^[121] found significantly elevated levels of 6-keto-PGF_{1α}, a metabolite of prostacyclin, in cirrhotic patients with PHG in the serum and in mucosa of the gastric fundus.

20. Page 20, line 24 - change 'endothelial' to 'epidermal'

Response

CHANGED TO:

The gastric concentrations of EGF (epidermal growth factor)

FROM:

The gastric concentrations of EGF (endothelial growth factor)

21. Page 21, line 7 - suggest changing 'any correlation' to 'such correlation'

Response

CHANGED TO:

did not show this correlation.

FROM:

did not show any correlation.

22. Page 21, line 12 - esophagogastroduodenoscopy (EGD)

Response

CHANGED TO:

PHG is diagnosed by esophagogastroduodenoscopy (EGD)

FROM:

PHG is diagnosed by EGD

23. Page 21, line 15 - incomplete sentence

Response

CHANGED TO:

The red lesions vary in size and in color depending on PHG severity. The lesions range from pink speckled lesions within a mosaic or snakeskin pattern in mild cases, to localized small areas of intense erythema, resembling a scarlatina rash, in severe cases

FROM:

The red lesions vary in size and color, ranging from pink speckling within a mosaic or snakeskin pattern in mild cases, to localized small areas of intense erythema resembling a scarlatina rash in severe cases

24. Page 21, line 28 - 'is best' to 'is the best'

Response

CHANGED TO:

which classification is the best

FROM:

which classification is best

25. Page 22, line 11 - fix (17,, 18,, 8)

Response

CHANGED TO:

HPG^[8,17,18].

FROM:

HPG (17,, 18,, 8)

26. Page 22, line 15 - '.2 mm' to '2 mm'

Response

CHANGED TO:

defined as red, 2-mm-wide, round lesions

FROM:

defined as red, .2-mm-wide, round lesions

27. Page 23 - bold 'Capsule endoscopy'

Response

CHANGED TO:

Capsule endoscopy

FROM:

'Capsule endoscopy

28. Page 24 - bold 'Dynamic CT'

Response

CHANGED TO:

Dynamic CT

FROM:

Dynamic CT

29. Page 24, third paragraph - be consistent with font used in text

Response

CHANGED TO:

12 Font

FROM:

11 Font

30. Page 25, line 14 - 'Differential of varices from PHG as the etiology of bleeding'

Response

CHANGED TO:

Differentiating GI bleeding from varices versus PHG

FROM:

Differentiation of esophageal varices from PHG as the etiology of bleeding

31. Page 26, line 9 - 'PHG (54),' to 'PHG (54).'

Response

CHANGED TO:

PHG^[54].

FROM:

PHG (54),

32. Page 26, line 22 - do not understand what does '59=original reference' mean

Response

CHANGED TO:

3) positive fecal occult blood (Baveno II)^[163].

FROM:

3) positive fecal occult blood ((Baveno II; 59=original reference, 163).

33. Page 27, last paragraph - change '..to arrest acute bleeding.' to '...to arrest acute bleeding from congested gastropathy.'

Response

CHANGED TO:
to arrest acute bleeding from PHG.
FROM:
to arrest acute bleeding.

34. Page 28, line 5 - misspell 'carvedilol'
Response
CHANGED TO:
the efficacy of carvedilol,
FROM:
the efficacy of carvediol,

35. Page 28, line 14 - Do the authors mean 'PHG (181)' instead of 'PHT (181)'?
Response
CHANGED TO:
portal pressure in PHG
FROM:
portal pressure in PHT

36. Page 28, last line - fix '((180)'
Response
CHANGED TO:
than vasopressin or omeprazole^[180].
FROM:
than vasopressin or omeprazole ((180)

37. Page 29, line 2 - 'et al,' to 'et al.'
Response
CHANGED TO:
Kouroumalis et al.^[175]
FROM:
Kouroumalis et al, (175)

38. Page 29, line 14 - intravenously (IV)
Response
CHANGED TO:
administered intravenously (IV)
FROM:
administered IV

39. Page 29, line 17 - delete '(180)'
Response
CHANGED TO:
that achieved by octreotide^[180].,
FROM:

that achieved by octreotide (180),

40. Page 30, line 18 - '(p<0.05,, w)hen' to '(p<0.05), when'

Response

CHANGED TO:

and catalase ($p<0.05$) when compared

FROM:

and catalase ($p<0.05,w$)hen compared

41. Page 30, line 19 - antioxidants.

Response

CHANGED TO:

Preoperative administration of vitamin E in the ligation group led to significantly increased levels of the three major antioxidant enzymes, including the levels of superoxide dismutase ($p<0.005$), glutathione peroxidase ($p<0.01$), and catalase ($p<0.05$), when compared to the levels of these antioxidant enzymes in untreated groups or in groups treated postoperatively with vitamin E. These data provide a theoretical basis that vitamin E administration may potentially improve PHG.

FROM:

Preoperative administration of vitamin E in the ligation group led to significantly increased levels of antioxidants, including superoxide dismutase ($p<0.005$), glutathione peroxidase ($p<0.01$), and catalase ($p<0.05$, w)hen compared to untreated groups or postoperatively treated groups with vitamin E. This was true for all three evaluated antioxidants:. These data provide a theoretical basis for vitamin E to improve PHG.

42. Page 30, second last paragraph - 'PHT' means 'PHG'?

Response

CHANGED TO:

Rats with PHG had a 2.3-fold increased area of gastric mucosal necrosis after gastric exposure to ethanol than sham-operated rats ($p<0.05$), but vitamin E treatment in rats with PHG almost completely reversed this increased necrosis compared to controls ($p<0.05$). Vitamin E treatment did not significantly change portal pressure or gastric mucosal blood flow in PHG gastric mucosa.

FROM:

Rats with PHT had a 2.3-fold increased area of gastric mucosal necrosis after gastric exposure to ethanol than sham-operated rats ($p<0.05$), but vitamin E treatment in rats with PHT almost completely reversed this increased necrosis compared to controls ($p<0.05$). Vitamin E treatment did not significantly change portal pressure or gastric mucosal blood flow in PHT gastric mucosa.

43. Page 31, line 12 - add units for the blood flow measurements

Response

CHANGED TO:

rats that underwent portal vein ligation as compared to placebo (56 ± 3.5 ml/min/100 gm for placebo; 43 ± 3.4 ml/min/100 gm for estrogen; 32 ± 2.6 ml/min/100 gm for dihydroxyprogesterone, and 42 ± 6.1 ml/min/100 gm for low dose estrogen/dihydroxyprogesterone, $p<0.05$).

FROM:

rats that underwent portal vein ligation as compared to placebo (56 ± 3.5 for placebo; 43 ± 3.4 for estrogen; 32 ± 2.6 for dihydroxyprogesterone, and 42 ± 6.1 for low dose estrogen/dihydroxyprogesterone, $p < 0.05$).

44. Page 32, second paragraph - (194; 195) to (194, 195)

Response

CHANGED TO:

stabilizing blood clots^[194,195].

FROM:

stabilizing blood clots (194; 195).

45. Page 33, line 20 - (30) to (30)

Response

CHANGED TO:

to decreasing portal hypertension^[30].

FROM:

to decreasing portal hypertension (30).

46. Page 33, line 26 - fix (30,)

Response

CHANGED TO:

Mezawa et al.^[30],

FROM:

Mezawa et al. (30,),

47. Page 34 - bold 'Other invasive therapies'

Response

CHANGED TO:

Other invasive therapies

FROM:

Other invasive therapies

48. Page 35, line 19 - 8 'gm/dL' to 'g/dL' and (186, 219; 220) to (186, 219, 220)

Response

CHANGED TO:

to maintain the hemoglobin level at 8 g/dL

FROM:

to maintain the hemoglobin level at 8 gm/dL

49. Page 35, line 19 - (186, 219; 220) to (186, 219, 220)

Response

CHANGED TO:

^[186,219,220].

FROM:

(186, 219; 220)

50. Page 36, line 18 - fix (220, 6, 158)..

Response

CHANGED TO:

and prevent chronic bleeding ^[6, 158,220].

FROM:

and prevent chronic bleeding (220, 6, 158)..

51. Page 37, first line - fix references

Response

CHANGED TO:

portal pressure^[175,180,185,231,232,233].

FROM:

portal pressure (175, 231; 232; 233; 175; 180; 185).

52. Page 37, line 12 - '1 [12.5%] of 8)' to '(1 [12.5%] of 8)

Response

CHANGED TO:

was much lower for PHG (1 [12.5%] of 8)

FROM:

was much lower for PHG 1 [12.5%] of 8)

53. Figure 1. What does the asterisk next to 'decreased gastric mucosal perfusion' stands for?

Response

ADDED TO FIGURE:

*The finding of decreased gastric mucosal perfusion in PHG is somewhat controversial (see text).

54. Page 40, Table I, reference 16 - fix the numbers

Response

CHANGED TO:

86 (9%)	56 (5.8%)	30? (3.1%)
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FROM:

86 (9%)	56? (64.8%)	30? (35.2%)
---------	-------------	-------------

55. Page 41, Table II, reference 18 - add the numbers next to percentages

Response

CHANGED TO:

PHG	mild	severe
362 (64%)	192 (34%)	170 (30%)

FROM:

PHG	mild	severe
(64%)	(34%)	(30%)

56. Page 42, reference 22 - 79.27% to 79.3%

Response

CHANGED TO:

172 (79.3%)

FROM:
172 (79.27%)

57. Page 42, reference 43 - fix the last two columns

Response

CHANGED TO:

49 (70%)	32 (46%)	17 (24%)
----------	----------	----------

FROM:

49 (70%)	32 (45%)	17 (24%)
----------	----------	----------

58. Page 48 - the criteria points should be put in the first column and the severity should be in the second-four columns

Response

CHANGED TO:

Please see Table VIII for revisions.

Reviewed by 00070481

The review may useful for the researcher and clinical doctors in the area of Portal hypertensive gastropathy

Authors' Responses.

No revisions required.

Other Changes

As per the editorial policy of the Journal:

1. The citations throughout the text have been changed to be placed in brackets and in superscript instead of in parenthesis.
2. The references throughout the paper have been changed to the World Journal of Hepatology format. In particular, all the references have been changed to include the DOI as well as PMID information.
3. We have enhanced this review by including an endoscopic photograph of the classic endoscopic findings in portal hypertensive gastropathy.

Thank you for the careful review by the reviewers and editors of this manuscript. Please inform us of any further revisions which we will gladly complete.

Warm regards,
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