

Response to peer-review comments from reviewer #1, Reviewer code 05084456

Name of journal: World Journal of Gastrointestinal Surgery

Manuscript NO: 69211

Title: Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

Reviewer's code: 05084456

SPECIFIC COMMENTS TO AUTHORS

The Authors reported expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia. This study is simple, but I think it is an important finding. However, some points should be discussed. Major comments 1. It is difficult to understand the definition of ISI from the text alone, can you please illustrate it? This will help the reader to understand it better as well. 2. The authors described "Our results didn't show a positive correlation between ghrelin and ghrelin receptor in adenomas with low grade dysplasia ($P < 0,05$)." in discussion. Isn't this a mistake for $p > 0,05$? 3. Do tumor growth factors by ghrelin, such as the ones you cited in your references 21 and 22, have a similarly heterogeneous expression in colorectal adenomas? This is important information to support the role of ghrelin in adenomas. Minor comments In Table 3, "SI for ghrelin receptor in adenoma" should be replaced by "ISI for ghrelin receptor in adenoma".

Respected reviewer,

Thank you for your valuable input and kind words regarding our study.

1. As you suggested we illustrated a bit better the ISI definition in the Methods part, as it is a number obtained by multiplication of the intensity of the reaction and the percentage of reactive cells (after staining for ghrelin and ghrelin receptor) based on which we could group the adenomas and adjacent tissue based on ghrelin and ghrelin receptor expression.
2. For the second comment on positive correlation of ghrelin and ghrelin receptor in adenoma with low grade dysplasia we really did not find a correlation. It can be seen in Table 3 where for adenomas with low grade dysplasia Spearman's rank correlation Rho was -0.108 and P value 0,459. Based on our current studies or other studies we cannot explain better our results since we did find a positive correlation between ghrelin and ghrelin receptor both in normal adjacent tissue and high grade adenomas.
3. We added in the Discussion a paragraph in the text regarding the expression of EGFR in low and high grade adenomas as well as the importance of PI3K-Akt pathway.
4. In Table 3 the typing error was corrected.

We hope that the changes made to the manuscript fulfill your expectations, and we believe that according to your suggestions we improved the quality of this manuscript.

Best regards.

Response to peer-review comments from reviewer #2, Reviewer code 05461079

Name of journal: World Journal of Gastrointestinal Surgery

Manuscript NO: 69211

Title: Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

Reviewer's code: 05461079

SPECIFIC COMMENTS TO AUTHORS

The study is interesting and fill within the scope of the journal. It is an observational study on the expression of ghrelin and ghrelin receptors in colorectal adenomas and adjacent tissues. Abstract: This sentence is not clear, suggest to reframe "This points out to the conclusion that in adenomas with high grade dysplasia we what was not found in adenomas with low grade dysplasia". Introduction: Ghrelin receptor was found to be highly expressed in adipose tissue and its activation influences the differentiation and proliferation of adipocytes and decreases apoptosis what is mediated through MAP/PIP 3/Akt pathway[6]. do you mean adipocytes? Please correct. Results: Figure 2, add receptor to the description under the table Table 2: indicate what Yes and No means under the table. Table 3: indicate what P, N, Rho under the table. Discussion: The results are repeated under this section, which is not required. Instead, need to write more on other similar studies, and justify the differences between your findings and their findings. Need to explain the result part related to the expression of ghrelin and ghrelin receptors on the adjacent tissues. The similar studies and the significance of these findings. The discussion part will benefit from adding the strengths and weakness of the study as well as limitations. You may add a paragraph on the significance and impact of this study. Throughout the manuscript, there are sentences that are not clear in meaning and require editing. Thank you.

Respected reviewer,

Thank you for your valuable input and kind words regarding our study.

1. As you suggested that the sentence in the Abstract part Results was not clear enough we found that after revision it better suited in the Conclusion. Since the Conclusion part is limited to 30 words we had to remove it completely.
2. In the Introduction the sentence that is connected to the reference no 6 was rephrased to be clearer.
3. In Figure 2 we corrected the typing error and added receptor to the description under the figure.
4. In Table 1 you addressed the issue of what Yes and No means, we acknowledge that this was not maybe clear enough for the reader so we altered the table for this to be more understandable.
5. In Table 3 we indicated what P, N and Rho represent under the Table.
6. According to your suggestions we removed the results that were repeated in this section that did not serve its purpose in explaining the connection with other studies. We added studies on colorectal adenomas that explored the same pathways (EGFR, PI3K/ Akt) involved also in ghrelin signaling. Until the point of writing this letter, searching relevant publication databases, there haven't been published any studies on ghrelin expression in colorectal adenoma. There has been only one review concerning ghrelin in colorectal neoplasias that has been published in 2021 and that we now cited. This is one of the reasons we believe that this is an important study and are looking forward to further studies from other researcher on this subject.
7. In the discussion part we added a section on the strengths and weakness of this study.
8. The manuscript was once more after all alterations suggested from you and other peer reviewers reviewed and corrected by a native English speaker.

We hope that the changes made to the manuscript fulfill your expectations and we thank you for all the suggestions.

Best regards.

Response to peer-review comments from reviewer #3, Reviewer code 03656608

Name of journal: World Journal of Gastrointestinal Surgery

Manuscript NO: 69211

Title: Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

Reviewer's code: 03656608

SPECIFIC COMMENTS TO AUTHORS

Ghrelin is an orexigenic peptide produced and secreted predominantly in the gastrointestinal tract but also in a range of normal cell types and tumors. In the manuscript, the author was aimed to investigate the expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and adjacent colorectal tissue. The objective of this study is interesting, but the experiment was not necessarily very well designed. As of now there is really not much novel about this manuscript to justify its publication as a full length paper. The authors could have done a better job in explaining their current findings. 1) Abstract: The abstract should be stated briefly and succinctly. RESULTS---Do not interpret the data here. Do not explain how you deduced the conclusion from the results obtained. 2) Introduction----The rationale of the study is not sufficiently explained. 3) This work would be strengthened if the authors could include some in vivo and vitro work to tie together all the pieces of the proposed mechanism. 4) Figure 3 and Figure 4: The statistical labeling of the bar graph figures needs some further detail. Statistical tests and statistical significant differences should be should be indicated on the figures.

Respected reviewer,

Thank you for your review and suggestions that we have taken in account while revising our manuscript. There are several points that we would like to explain.

1. A recently published review article by Spiridon *et al.* on Ghrelin and its role in gastrointestinal tract tumors states that although ghrelin was found to be expressed in several tissues and tumors there is insufficient data to be confident to explain the all the exact mechanism in which ghrelin influences gastrointestinal tract tumor progression and that new studies are needed to give more light on this problem. As until now, no study was published on expression of ghrelin and its receptor in colorectal adenoma, therefore we find our study, although simple, significant in giving new insight into this subject. We are definitely not confident enough to claim that there is nothing more to say on this subject.
2. In the Results segment of the Abstract we removed according to your suggestions the part where we interpreted the data. As for the length of the abstract it was written according to instructions for Abstract writing in Observational Study given by BPG Publishing.
3. According to your suggestions we added in the Introduction part of the Main manuscript results from other studies and our points for conducting this type of study.
4. We are sorry if you missed in the Discussion part the in vivo and in vitro studies from other authors that were stated and that could explain the proposed mechanisms of ghrelin actions. We added in the Discussion a paragraph in the text regarding the expression of EGFR in low and high grade adenomas as well as the importance of PI3K-Akt pathway which were already stated as vital pathways through which ghrelin expresses its activity in progression of tumors.

5. We added in Figure 3 and Figure 4 as you suggested the labeling of the y axis for better understanding.
6. Statistical tests and differences are described extensively in the manuscript text and according to BPG Guidelines for Manuscript Preparation and Submission: Observational Study Sections 2.4, 2.5 and 2.6 we have prepared both the Tables and Figures and their Notes without the duplication of information in the manuscript and the Tables/Figures.

We hope that the changes made to the manuscript fulfill your expectations and we thank you for all the suggestions.

Best regards.