



Santander. April 17, 2015

Dear Editor,

Please find enclosed the edited manuscript.

Title: Plasma betatrophin levels in patients with liver cirrhosis

Authors: Maria Teresa Arias-Loste, Maria Teresa García-Unzueta, Susana Llerena, Paula Iruzubieta, Angela Puente, Joaquín Cabezas, Carmen Alonso, Antonio Cuadrado, José Antonio Amado, Javier Crespo, Emilio Fábrega

Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated and is highlighted in the attached reviewed file. Files related to academic rules and norms included in BPG's Revision Policies for Retrospective Study document have been added.
2. Revision has been made according to the suggestions of the reviewers:

(1) The paper Arias-Loste and collaborators, this well presented. It is an excellent work on betatrophin in cirrhotic patients and its relationship to the severity of the disease. Congratulations.

We thank the comments and the effort reviewing our paper.

(2) Maria Teresa and her colleague highlighted the important relation between Betatrophin and cirrhosis. This study is so important, especially because many scientists and clinicians world wide want/ would like to support MELD score with supportive lab such Na and proteins such as Betatrophin prior to Liver Transplantation, or even in follow patients up. The study is normal extension of Melton DA novel work about Betatrophin, however this extension is vitally important, additionally it will open/ support

the future publication competition related- cirrhosis and circulating harming proteins. The language is amazing with professional style.

We appreciate this kind comments and the effort reviewing our paper.

(3) In this study, the authors measured plasma betatrophin levels in patients with liver cirrhosis and examined the relationships among betatrophin levels, insulin resistance (IR), and liver function. The results suggested that plasma betatrophin levels were significantly associated with IR and liver function. The Reviewer has the following comments. Major points. 1. To more clarify the relationship between plasma betatrophin levels and liver function, the authors should include patients with Child-Pugh class A liver cirrhosis. 2. The interpretations of the results in this study are difficult unless the relationship between IR and liver function will be clarified. If there is a significant relationship between the two, the authors should examine the relationship between plasma betatrophin levels and IR by matching liver functions of the patients. Similarly, they should examine the relationship between plasma betatrophin levels and liver function by matching the degrees of IR of the patients. Minor points. 1. Please correct some errors in the text (e.g. Bonferroni adjustment was performed).

We thank the comments and suggestions. We agree that it would be of great interest to include an additional group of patients with Child-Pugh class A. Unfortunately, we do not have patients with this characteristics in our cohort. We believe that, according to the significant differences between cirrhotic patients and healthy controls and to the strong association between betatrophin levels and disease severity, although it would be desirable to count of the participation of Child-Pugh class A patients, our results could be considered valid.

Regarding the second comment, we have re-analysed our data and found that there is a significant association between the coexistence of insulin resistance and liver function measured according to Child-Pugh's classification ($p=0.001$). In this regard, we have considered as well the suggestion of a new analysis regarding the association between betatrophin and IR clustered by liver function, and between betatrophin and liver function according to the presence of insulin resistance. In this sense, this new analysis shows how betatrophin levels are significantly higher in patients with insulin resistance irrespectively of liver function, but with more significant differences in advanced liver disease. Finally, betatrophin levels are higher in patients with more severe liver disease and insulin resistance in contrast to patients without insulin resistance.

We have corrected the grammatical errors pointed out.

Thank you again for taking our manuscript into consideration for publication in the *World Journal of Gastroenterology*.

Best regards,

A handwritten signature in black ink, appearing to read 'E. Fábrega', written in a cursive style.

Emilio Fábrega García, MD, PhD.

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