

Format for ANSWERING REVIEWERS

December 20th, 2013



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7245-OA.doc).

Title: Subclinical abnormal glucose tolerance is a predictor of death in liver cirrhosis

Author: Diego García-Compeán, Joel Omar Jáquez- Quintana, Fernando Javier Lavallo-González, José Alberto González-González, Linda Elsa Muñoz-Espinosa, Jesús Zacarías Villarreal-Pérez, Héctor J Maldonado-Garza

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7245

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1: 00068518

- 1.- The number of recruited patients for the study, and the mean length of follow up, were added in the section of METHODS of the abstract.
- 2.- The phrase "in a previously published study by our team....." was deleted, since we considered that it was unnecessary.
- 3.-The paragraph including the phrase "However these findings..." was modified according to reviewer's comments.
- 4.-The reasons for following the selection criteria used in the study were discussed in the text.
- 5.- Some references proposed by the reviewer were included in the introduction section

of the manuscript.

6.- References regarding clinical diagnosis of cirrhosis were added in the METHODS section of the text.

7.- The methods for determining the etiology of LC were included in the text

8.- An explanation that BMI is not an appropriate method for assessing nutritional status in patients with liver cirrhosis and ascites was included in the text.

9. - The sentence "The primary end point of our study was the occurrence of death" was deleted since we considered that it was not necessary.

10.-A flowchart describing selection of patients for the study was included in the text as figure 1.

11.- Description of the proportion of patients who stopped drinking alcohol, and those with viral or autoimmune etiology who received specific treatment, was added to the text. The effects of antiviral drugs or corticosteroids on glucose metabolism were not analyzed given the short number of patients in each group.

12.- The first paragraph of the discussion section was deleted.

13.- In conclusions, we suggest performing OGTT in all non diabetic cirrhotic patients for assessing prognosis only . Its use for early detection of DM, in order to start early treatment, may be an obvious objective. Nevertheless, currently it is not known if early diagnosis and treatment of subclinical or clinical DM modifies the evolution of liver cirrhosis (we discuss this issue in the manuscript).

14.- In the text, we added a discussion concerning the reasons by which we did not use HbA1c testing for diagnosis of abnormal glucose tolerance and gave a reference.

15.- Discussion of recent publications regarding the frequency of cardiovascular complications and atherosclerosis in patients with chronic liver disease was developed.

16.-Mechanistic reasons for explaining the association between DM and hepatic encephalopathy were briefly discussed

17.-Figure legends were modified according to reviewer's comments

18.- The title of the manuscript was partially modified

19.- In the abstract the word "notorious" was substituted by the word "evident".

Q1.- In fact, we have published studies regarding prevalence of subclinical abnormal glucose tolerance in non diabetic compensated cirrhosis. We have found a prevalence of 66% (ref 18). The figure of 50% in the text is a mistake. Therefore we have corrected the figures in the text.

Q2.- We describe in the section of follow up the proportion of patients who stopped drinking alcohol (47%). The figures were similar in both groups.

Q3.- In the same section we describe proportion of patients with viral hepatitis who received antiviral treatment (47% for C and 50 for B). 90% of patients with autoimmune etiology received treatment .The figures were also similar in both groups.

Q4.- We are sorry for suppressing data in the box of table 1 concerning number of patients with HBV in the group of abnormal glucose tolerance. We have corrected the table.

Reviewer 3: 02861137

We have read with interest the comments of Reviewer 3 concerning our manuscript. They made us to suppose that the content of our text was misunderstood by him (her).

As the main point of concern of our manuscript he/she writes: "refers to definition of the subclinical abnormal glucose tolerance". And continues: "According to the guidelines of the American Diabetes Association (ADA) patients with a 2-hour plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test as considered has having diabetes mellitus"

In fact , the term that we used in our text "abnormal glucose tolerance" included impaired glucose tolerance and DIABETES MELLITUS, that were detected with OGTT. Both are, in practical terms, abnormal glucose tolerance conditions or abnormal OGTT. The term "subclinical" was used in order to underline that IGT and DM were only detected by using OGTT.

Concerning other points:

Sample size of patients was not big in our study. Taking into account number of patients

in our study, multivariate regression testing Cox's proportional hazard model ,that we used for evaluating independent predictors of death, is the best. Stratification of groups for analysis may be inadequate since an "atomization "of groups may reduce power of statistical tests.(e.g. group of treated patients with HBV is composed of 2 , treated HCV patients are 6, etc)

English of the text was reviewed by an expert

Only patients with DM (not IGT) were treated with antidiabetic drugs or insulin including those who developed DM during follow up. (This statement was already included in the text)

Most patients died in the hospital. Causes of death were determined by our physicians.

P values of Table 1 were not given since most of differences were not significant

In table 2 it was defined that comparison were performed with Chi test.

In table 3 proportions of died patients were corrected.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Diego Garcia Compean MD MMSc

Gastroenterology Service and Department of Internal Medicine.University Hospital "Dr. Jose E. González"and Faculty of Medicine. Universidad Autónoma de Nuevo León. Madero y Gonzalitos S/N, Monterrey NL. México Email: digarciacompean@prodigy.net.mx

Telephone: +52-81-83487315 **Fax:** +52-81-89891381