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Dear Editor,

We would like to thank you and the reviewers for the comments and suggestions that helped us to improve our manuscript entitled: **Predictors for Advanced Fibrosis in Morbidly Obese non-alcoholic Fatty Liver Patients**. ESPS manuscript NO: 29360

We have responded very carefully to each of the comments. All the changes made in the original manuscript appear as **underlined bold** in the revised manuscript.

We hope that you find our revised manuscript suitable for publication.

Sincerely yours,

Sincerely yours,

Sigal Fishman MD

Director of Obesity Service

Gastroenterology Department

Tel-Aviv Medical Center

pls see

The following is our point-by-point response to the reviewers' comments.

Reviewer 1

How many patients with ALT elevation? Does ALT level not influence liver stiffness?

Response: 17 patients had elevated ALT. There was no association between ALT and fibrosis (correlation $r=0.17$. $P=0.253$), but it may be due to the small sample of people with elevated ALT and therefore this was not included in the manuscript.

Do authors analyze patients with ALT elevation compare with whom ALT in normal range?

Response: Due to the small sample of people with ALT measurement and more so with elevated ALT this was not included in the manuscript. Either way, as mentioned above, ALT was not correlated with liver fibrosis nor there was a significant difference between those with elevated ALT and those with normal ALT in the mean levels of liver stiffness (10.3 ± 7.0 in normal vs. 12.1 ± 7.0 in elevated ALT group, $P=0.394$).

In this study, there are only 47 patients with ALT level. This is a small sample size.

Response: We agree it's one of the disadvantages of the study.

The authors have not analyzed and discussed ALT level impact among groups and fibro stages. The ALT level may have important role in this study.

Response: Following this comment we added to the manuscript the correlation between serum ALT levels and liver stiffness (in the results section on page 11).

For smoking factor analyzed in fig 3, the $r^2=0.29$, so it is hardly to get the conclusion smoking is a risk factor for advanced disease in this study.

Response:

We agree with this comment that the correlation coefficient is not very strong, although explaining 30% of the variance in fibrosis level is still not negligible in an outcome that obviously effected by many factors. We no added to the conclusion that "The suggested association with the degree of smoking in men will have to be confirmed in further studies".

Reviewer 2

The study of Shira et al. aimed to examine predictors of liver fibrosis in extremely obese NAFLD patients. Their study is of great clinical importance, well-designed and well-

presented. Minor comments that needs revision: - reference 23 is not proper, please change it to a proper one.

Response: Thank you. Reference 23 was replaced by references of studies among NAFLD patients.

What can be the explanation of the predictor characteristic of cigarette smoking and liver fibrosis in obese men? After minor revision, I suggest to accept the manuscript for publication.

Response:

To the best of our knowledge, there is no explanation of the predictor characteristic of cigarette smoking and liver fibrosis in obese men. There are explanations to the effect of smoking of fibrogenesis as described in the discussion section, but not specifically in men. It may be that since men are heavier smokers and have more fibrosis, the association among men was more prominent in a study of a small sample size with a few heavy smoking women. Other studies will have to confirm these results as indicated now in the discussion section.

Reviewer 3

This is an interesting and well-organized study. The results are clearly presented. The authors should address the following minor comments:

Please provide the number of patients in whom blood tests were available.

Response:

This is now added to the text of the methods in “Demographic, health and lifestyle data” on page 9 and also was indicated for each test in the table itself (table 1).

Reference 23 refers to patients with hepatitis C.

Another study in patients with NAFLD should be used to define cutoffs for fibrosis stages.

Response:

Thank you for the comment, the reference was changed accordingly to studies among NAFLD patients.

The authors should mention that cigarette smoking was not an independent predictor of advanced fibrosis in multivariate analysis. Indeed, cigarette smoking correlated with fibrosis in men only, suggesting that the association between smoking and fibrosis is driven by the higher percentage of smoking among men, who are at increased risk for fibrosis. Therefore, the suggestion that smoking cessation might reduce the risk for advanced fibrosis is not supported by the presented data and should be removed.

Response:

The association between smoking and fibrosis may be easier to demonstrate among men since they have higher fibrosis level and higher cigarette consumption level in

contrast to women with few heavy smokers and less fibrosis, but it still does not cancel the observation that among men themselves there is an indication for association with the amount of smoking. A proper multivariate analysis cannot be performed in such a small sample of smokers (“twenty one of the men and 16 of the women were current or past smokers”). However, we agree with the flows of this study in that topic, and thus we modified the conclusion to a more careful one and removed the sentence on smoking cessation from the “Core tip”: section.

The authors should mention that Fibroscan has limited accuracy in morbidly obese patients.

Response:

Thank you, we added this limitation to the discussion section with a new reference.