



## Correspondence

## Reply to: “Hepatic fibrosis – and not steatosis – is the main determinant of arterial stiffness in non-alcoholic fatty liver disease”



## ARTICLE INFO

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## To the Editor,

We appreciate the interest in and comments to our recent paper [1]. In their letter, Yilmaz and Eren raised two issues, a possible association between hepatic fibrosis – and not steatosis – and arterial stiffness in non-alcoholic fatty liver disease, and the use of wedge liver biopsy instead of a needle biopsy. Although the hypothesis of an independent systemic effect of liver fibrosis on arterial stiffness seems plausible, in our opinion it has not been supported yet by unequivocal scientific evidence. To address this issue and provide the requested data, we re-analyzed our study population of bariatric patients with regard to fibrosis stage by liver biopsy and its potential association with aortic pulse wave velocity (aPWV). The stage of fibrosis was categorized using the histological scoring system reported by Kleiner et al. [2]: stage 0 – no fibrosis, 1A – mild perisinusoidal fibrosis, 1B – moderate perisinusoidal fibrosis, 1C – isolated periportal fibrosis, 2 – presence of perisinusoidal and periportal fibrosis, 3 – bridging fibrosis, and 4 – cirrhosis.

In 38 patients without steatosis (less than 5% of hepatocytes with lipid infiltration), stage 0 was found in 4 patients (10%), stage 1A, B or C in 31 patients (82%), stage 2 in 3 patients (8%), and stage 3 in no patient. In 82 subjects with steatosis, stage 0 was found in 6 patients

(7%), stage 1 in 53 patients (65%), stage 2 in 18 patients (22%), and stage 3 in 5 patients (6%). No stage 4 fibrosis was found in any of our patients. For further analysis, the severity of fibrosis was considered a dichotomous variable: no or mild fibrosis (stages 0 and 1) versus moderate to severe fibrosis (stages 2 and 3).

In the overall study group, multivariate regression analysis did not show an independent association of the presence of moderate to severe fibrosis with aPWV (ln-transformed, for explanation see “Statistical analysis” in our original paper [1]) (Table 1). In the steatosis group, we found no significant difference in aPWV between patients with no or mild fibrosis (median [interquartile range] aPWV 6.72 [6.3–7.5] m/s) and those with moderate to severe fibrosis (aPWV 7.10 [6.44–8.41] m/s,  $p = 0.17$  by the Mann-Whitney  $U$  test). In addition, aPWV was not associated with the severity of fibrosis in multivariate linear regression model (Table 2).

Thus, we conclude that in our patients with morbid obesity, there was no independent association between liver fibrosis stage and aortic stiffness, although it should be noted that in most of our patients, the degree of fibrosis was mild. These findings cannot support a notion that hepatic fibrosis is the main determinant of arterial stiffness in non-alcoholic fatty liver disease.

Table 1

Multivariate linear regression analysis of aPWV as a dependent variable in the overall study group (n = 120).

aPWV (ln) dependent variable, adjusted $R^2 = 0.56$			
Variable	Regression coefficient (CI)	Standardized regression coefficient (CI)	p value
Age	0.008 (0.005–0.010)	0.472 (0.340–0.605)	< 0.001
MAP	0.007 (0.005–0.009)	0.402 (0.264–0.540)	< 0.001
HR	0.003 (0.001–0.005)	0.181 (0.051–0.311)	0.007
Fibrosis stage $\geq 2$	0.009 (–0.015 to 0.034)	0.050 (–0.080 to 0.179)	0.447
Diabetes	0.034 (0.010–0.058)	0.185 (0.055–0.316)	0.006
Female	–0.001 (–0.023 to 0.209)	–0.005 (–0.138 to 0.128)	0.937

aPWV, aortic pulse wave velocity; CI, confidence interval; HR, heart rate; MAP, mean arterial pressure.

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**Table 2**

Multivariate linear regression analysis of aPWV as a dependent variable in patients with liver steatosis (n = 82).

aPWV (ln) dependent variable, adjusted R <sup>2</sup> = 0.60			
Variable	Regression coefficient (CI)	Standardized regression coefficient (CI)	p value
Age	0.007 (0.004–0.009)	0.428 (0.275–0.581)	< 0.001
MAP	0.008 (0.005–0.011)	0.471 (0.308–0.633)	< 0.001
HR	0.003 (0.001–0.005)	0.197 (0.041–0.353)	0.014
Fibrosis stage ≥ 2	–0.007 (–0.033 to 0.019)	–0.042 (–0.196 to 0.104)	0.592
Diabetes	0.047 (0.019–0.075)	0.262 (0.105–0.419)	0.001
Female	–0.007 (–0.030 to 0.016)	–0.046 (–0.196 to 0.104)	0.545

aPWV, aortic pulse wave velocity; CI, confidence interval; HR, heart rate; MAP, mean arterial pressure.

Regarding the other raised issue, i.e., use of wedge liver biopsy instead of a needle biopsy, we agree that these two procedures may produce discrepant results and should not be directly compared. However, although the former is indeed limited to the surgical setting, it provides 20- to 40-fold larger histological sample compared to needle biopsy and thus may be more representative of the liver tissue as a whole [3], and the pathologist involved in the study was well aware of the need to disregard the subcapsular area in the histological evaluation of liver steatosis and fibrosis.

**Conflict of interest**

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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