Diabetes is the strongest risk factor of hepatic fibrosis in lean patients with non-alcoholic fatty liver disease

We read the commentary by Francque and Wong[1] with great interest. They pointed out that metabolic dysfunction could be the main factor associated with an increased risk of hepatic fibrosis among lean patients with non-alcoholic fatty liver disease (NAFLD). However, it is unclear whether the definition of metabolic dysfunction would also fit lean patients, who are less likely to have metabolic risks.[2] Herein, we evaluated the fibrosis burden in lean patients with NAFLD according to the presence of each metabolic dysfunction component.

We analysed participants in a community-based cohort, all of whom have undergone magnetic resonance elastography (MRE) for their health check-up (N=6775, 100% single ethnic Korean). Fatty liver was diagnosed by ultrasonography. The prevalence of NAFLD and lean (body mass index <23) NAFLD in all subjects was 35.2% and 3.7%, respectively. The mean liver stiffness value was lower in lean patients with NAFLD than in non-lean patients (2.26±0.55 vs 2.39±0.53, p<0.001) (online supplemental table 1). However, there was no difference in the prevalence of both significant (MRE ≥3.0 kPa) and advanced (MRE ≥3.6 kPa) fibrosis. Lean patients with NAFLD were older, more likely to be female, and had lower body mass index and waist circumference. In addition, lean patients with NAFLD showed lower alanine transaminase and triglyceride levels and higher high-density cholesterol levels than non-lean patients. Interestingly, the prevalence of metabolic syndrome was lower in lean patients with NAFLD than in non-lean patients (7.1% vs 30.6%, p<0.001), and the prevalence of diabetes (11% in lean NAFLD vs 12.9% in non-lean NAFLD, p=0.402) did not differ between the two groups.

The mean values of liver stiffness did not differ according to the number of metabolic risks or presence of metabolic syndrome (figure 1). Nevertheless, it is noteworthy that the liver stiffness value was significantly higher in patients with diabetes. In addition, the proportion of patients with significant fibrosis (17.9% vs 4.9%, p=0.008) and advanced fibrosis (17.9% vs 1.8%, p<0.001) was higher when compared between the groups with and without diabetes among the lean patients with NAFLD. In line with this finding, the presence of diabetes alone was an independent risk factor for hepatic fibrosis, according to univariate and multivariate analyses (table 1). Other risk factors for metabolic syndrome were not predictive of significant/advanced hepatic fibrosis. A recent meta-analysis[3] indicated that diabetes is a more potent risk factor for severe liver disease in patients with NAFLD than obesity or metabolic syndrome. Nevertheless, we should be cautious on the fact that diabetes does not necessarily mean causal relationship with fibrosis.

Table 1 Multivariate logistic regression for significant or advanced fibrosis in lean patients with NAFLD

Variables	OR	95% CI	P value
Significant fibrosis			
Hypertension	0.367	0.075 to 1.799	0.217
Diabetes	4.291	1.284 to 14.346	0.018
Low HDL or dyslipidaemia medication	1.114	0.317 to 3.911	0.866
Central obesity	0	0	0.999
High triglyceride	1.767	0.609 to 5.128	0.295
Advanced fibrosis			
Hypertension	0.26	0.028 to 2.441	0.238
Diabetes	13.833	3.195 to 59.897	<0.001
Low HDL or dyslipidaemia medication	0.691	0.121 to 3.947	0.678
Central obesity	0	0	0.999
High triglyceride	2.052	0.484 to 8.707	0.33

P values were calculated through analysis of the logistic regression model for hypertension, diabetes, low HDL or dyslipidaemia medication, high triglyceride, and central obesity.
Definition of abnormality: (1) hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or hypertensive drug medication; (2) diabetes: fasting plasma glucose level ≥126 mg/dL, glycated haemoglobin level ≥6.5% and/or current use of antihyperglycaemic medications; (3) low HDL-cholesterol level: <40 mg/dL for men and <50 mg/dL for women; (4) central obesity: waist circumference ≥90 cm (men) and ≥80 cm (women); and (5) high triglyceride level: ≥150 mg/dL.
HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease.

There are several limitations. First, men were predominant in our cohort, which reflects some selection bias or at least limited generalisability. Nevertheless, we assume that the large number of women (n=1315) and the representative characteristics of our nationwide data render sufficiency for ensuring adequate statistical power. Second, there is ambiguity between metabolic syndrome and metabolic dysfunction in our study on lean subjects. Nevertheless, there is no consensus on the definition of metabolic dysfunction for lean subjects. Francque and Wong[1] have also pointed out the

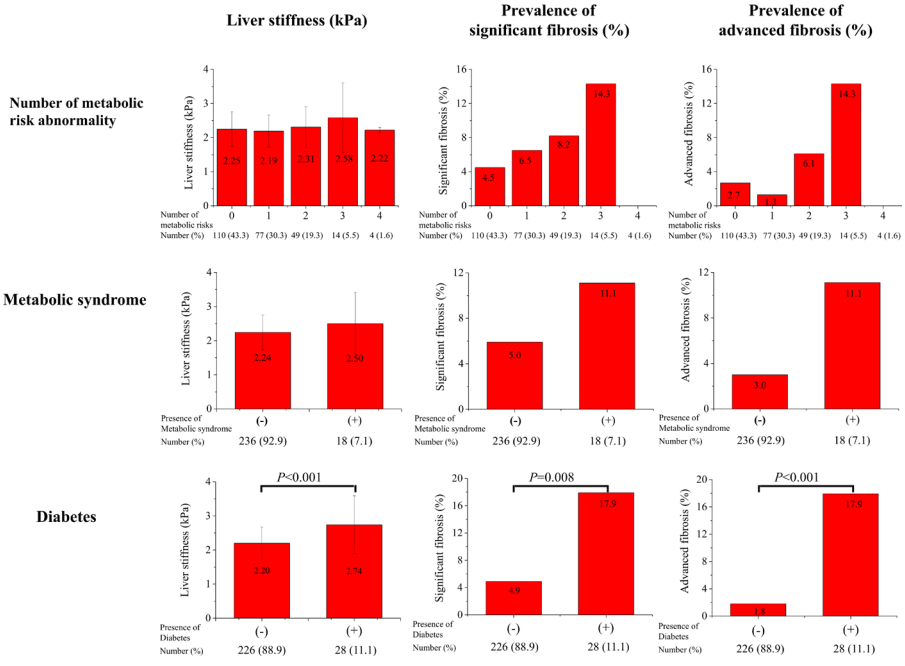

Figure 1 Hepatic fibrosis in lean patients with NAFLD according to metabolic abnormality or presence of diabetes. NAFLD, non-alcoholic fatty liver disease.

misconception on the term 'lean', which generally indicates metabolically healthy condition. Therefore, we think that the presence of diabetes in these lean patients would be a good indicator of not only the presence of metabolic dysfunction but also the presence of hepatic fibrosis.

In summary, lean patients with NAFLD who have a lower number of metabolic risks showed a non-negligible prevalence of diabetes similar to that in non-lean patients with NAFLD. The presence of diabetes is the most specific predictive (but not necessarily causative) factor for hepatic fibrosis in lean patients with NAFLD.

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