Reply to: "Seladelpar in patients with primary biliary cholangitis: Need for a closer look!"

To the Editor:

We thank Drs. Mishra and Singh for their interest in our paper[1] in which seladelpar, a potent and selective PPARδ agonist, demonstrated dose-dependent improvements in markers of cholestasis and inflammation[1] and would like to clarify the 4 issues that they raised.[2]

First, we agree that non-alcoholic fatty liver disease (NAFLD) is a common condition in adults which is likely to be present in a subset of individuals with PBC[3,4] and that a BMI >25 has been associated with steatosis or advanced fibrosis in PBC,[3] but we would also point out that this is not diagnostic of NAFLD and that BMI is only weakly correlated (0.46) with histological steatosis.[4] Teasing out a secondary benefit of seladelpar in patients with PBC and NAFLD would require more than simply monitoring liver stiffness and controlled-attenuation parameter values as suggested. Rather, it would require a study design similar to that done for seladelpar in patients with biopsy-proven non-alcoholic steatohepatitis[5] with the added requirement that participants have PBC with an incomplete biochemical response to ursodeoxycholic acid.

Second, although the mean alkaline phosphatase (ALP) was slightly higher in the 5 mg compared to the 10 mg dose group, there were comparable numbers of individuals with cirrhosis in each group, 14 in the 5 mg and 11 in the 10 mg groups. The percent change in ALP from baseline to Week 12 for the 5 mg and 10 mg groups was −34.5% (n = 47) and −43.2 % (n = 51), respectively, in this study and was nearly identical to that of a subsequent phase III study[6] where the corresponding change through Week 12 was −35.7% (n = 54) *vs.* −44.2% (n = 53) (p = 0.0013 for 5 mg *vs.* 10 mg). In this second study, the baseline ALP were well matched between groups at 290 and 291 U/L, respectively.

Third, we are baffled by the assertion that seladelpar might induce pruritus. PPAR agonists have previously been noted to relieve pruritus and we refer Drs. Mishra and Singh to a recently published sub-analysis evaluating the impact of seladelpar on pruritus; seladelpar clearly improved itch (reduction in pruritus VAS of ≥20) in patients with significant baseline pruritus VAS (≥40).[7] The improvement in pruritus with seladelpar was confirmed in the subsequent placebo-controlled study.[6]

Finally, we agree that seladelpar might have utility as first-line therapy, but this would require a head-to-head comparison of seladelpar to UDCA. The currently accepted surrogate endpoints utilizing ALP and total bilirubin[8] have been developed in UDCA-treated patients and have not been validated in UDCA-naïve patients in a contemporary setting. The validity of these surrogates would require further justification and/or evidence of improvement in clinical outcomes.

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Conflict of interest

Christopher Bowlus has received grants from Arena Pharmaceuticals, Cara Therapeutics, Genfit, Genkyotex, and Novartis and grants and personal fees from CymaBay Therapeutics, Eli Lilly, Gilead, GlaxoSmithKline, and Intercept. Cynthia Levy has received grants from Genkyotex, Gilead, High Tide, Intercept, Novartis, and Zydus and grants and personal fees from Cara Therapeutics, CymaBay Therapeutics, Genfit, and GlaxoSmithKline. Gideon M. Hirschfield has received personal fees from CymaBay Therapeutics, Genfit, GlaxoSmithKline, HighTide, Intercept Pharma, Mirum, and Pliant.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Drafting of the manuscript: CLB, CL, and GMH.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.024.

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Christopher L. Bowlus[1,*]
Cynthia Levy[2]
Gideon M. Hirschfield[3]
[1]*Department of Internal Medicine, University of California, Davis, Davis, California, United States*
[2]*University of Miami Miller School of Medicine, Miami, Florida, United States*
[3]*Toronto Centre for Liver Disease, University Health Network and Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

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*Corresponding author. Address: University of California, Davis, One Shields Ave, Davis, CA 95616, United States; Tel.: 916-734-0779, fax: 916-734-0804.

E-mail address: clbowlus@ucdavis.edu (C.L. Bowlus)

Associations of muscle mass and grip strength with severe NAFLD: A prospective study of 333,295 UK Biobank participants

To the Editor:

We read with great interest the study by Petermann-Rocha *et al.* which revealed the inverse associations of muscle mass and grip strength with the risk of developing severe non-alcoholic fatty liver disease (NAFLD) using 333,295 participants from the UK Biobank (UKBB).[1] Although this study has adjusted for several potential confounders including age, sex, deprivation, ethnicity, smoking, drinking, the components of metabolic syndromes and physical activity, the results can hardly be interpreted as causal associations.

Mendelian randomization (MR) design is an increasingly popular method of causal inference in epidemiology, which uses genetic variants as the instrumental variables to estimate the association between genetically predicted exposure on an outcome.[2] Since genetic variants are randomly allocated at conception, the MR design can be deemed as nature's randomization and can deduce the causal relationship. Previously, we reported that genetically predicted higher levels of low-density lipoprotein cholesterol could lower the risk of cholelithiasis using a MR design.[3] Herein, we attempted to answer whether the associations of muscle mass and grip strength with NAFLD were causal using the MR design.

Two sarcopenia-associated traits from the UKBB were included in this study, namely grip strength (right & left) and appendicular lean mass (ALM).[4] Three genome-wide association studies (GWASs) of NAFLD without UKBB participants were available, including a total of 3,724 cases and 285,622 healthy controls.[5,6] We estimated the causal effect on NAFLD in each NAFLD GWAS and combined the MR estimates using meta-analysis. A bi-directional 2-sample MR framework was developed and the multiplicative random-effects model was adopted to evaluate the causal effects. Besides, weighted median, MR-Egger and MR-PRESSO methods were adopted as sensitivity analyses.[7]

Explicitly, genetically elevated ALM and grip strength levels could decrease the risk of NAFLD in the FinnGen NAFLD GWAS, however, such causal associations were not significant in the other 2 NAFLD GWASs (Fig. 1). The meta-analysis of these MR estimates indicated that none of the genetically elevated sarcopenia-associated traits was causally associated with the risk of NAFLD (Fig. 1). It should be noted that genetically elevated ALM could marginally reduce the risk of NAFLD in the meta-analysis (odds ratio 0.961; 95% CI 0.921–1.002). The reverse MR analysis suggested the genetic predisposition to NAFLD could not affect the levels of grip strength and ALM. The weighted median and MR-Egger analyses also suggested the null associations between genetically predicted sarcopenia-associated traits and NAFLD. The MR-PRESSO methods detected outliers of ALM while the results were not significant after removal of them. There was neither heterogeneity nor horizontal pleiotropy in MR estimates (Cochranes's Q p value >0.05 and MR-Egger intercept p value >0.05). After adjusting for body mass index, type 2 diabetes, total cholesterol and blood pressure,

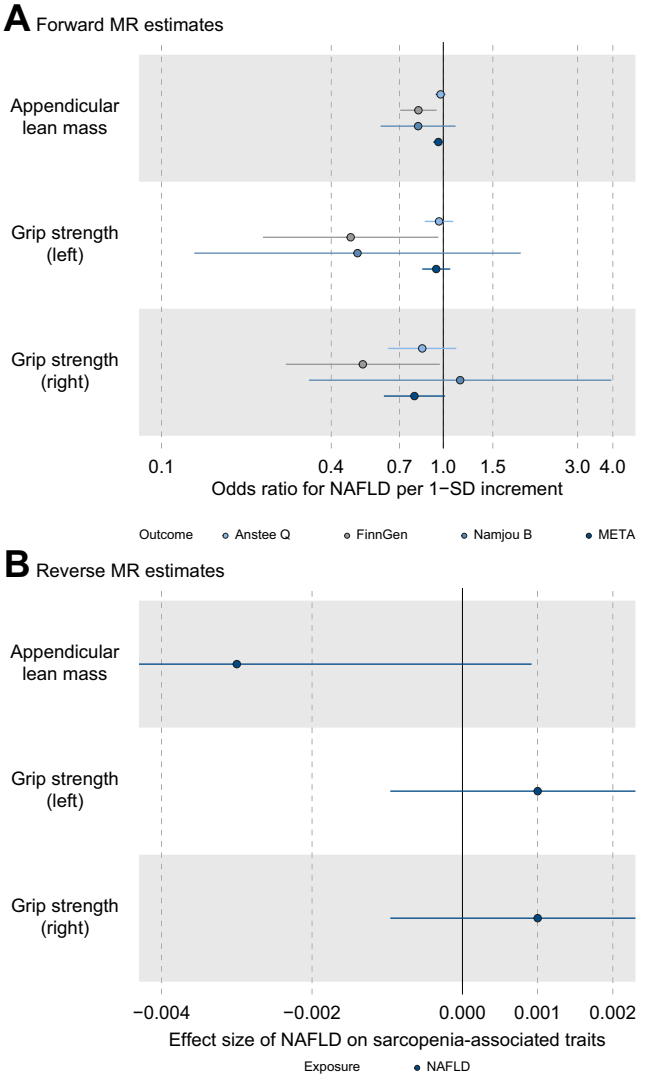

Fig. 1. The forest plot of forward and reverse MR estimates. (A) The outcome was NAFLD, and META represents the meta-analysis of MR estimates. (B) The effect size was beta value. NAFLD, non-alcoholic fatty liver disease; MR, Mendelian randomization.

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