JHEP|Reports

Reply to: "Reconsidering low HDL-cholesterol levels as a predictive factor for the development of hepatocellular carcinoma"

To the Editor:

We are grateful to Dr. Fujii and colleagues[1] for their interest in our study[2] and for taking the time to validate our findings and investigate the predictive role of HDL cholesterol (HDL-C) in the progression from liver fibrosis to hepatocellular carcinoma (HCC). We welcome this opportunity to discuss the rationale for assessing lipid profile and liver fibrosis as a prevention strategy for HCC.

In their letter, the authors suggest that the use of HDL-C level in HCC prediction may be premature, since in their population of Japanese patients with biopsy-proven NAFLD, HCC occurrence did not differ between groups of patients depending on HDL-C levels. Firstly, we believe that the identification of sub-populations in the study from Fujii *et al.* is quite different from ours. Indeed, from a methodological point of view, while they stratified the population according to HDL-C levels under or above 40 mg/dl, we first subdivided our sample according to liver fibrosis using APRI score ≥0.5, then we analysed the sub-population of patients with HDL-C ≤50 mg/dl to predict HCC, as shown in Fig. 5 of the original paper.[2] Nonetheless, in line with our findings, Fujii *et al.*[1] found that HDL-C levels were associated with advanced liver fibrosis, which is the fruitful crib for HCC.

Secondly, our results pointed not only to HDL-C levels, but also to waist circumference and fasting glucose levels (see Fig. 1A,C of the original study[2]) as anthropometric and bio humoral predictive biomarkers. Indeed, an important contributor to the overall pool of HDL-C could be adipose tissue, since adipocytes in culture have the ability to efflux cholesterol to HDL particles.[3] More specifically, the amount of visceral adipose tissue is related to increased systemic inflammation and cancer risk and may represent a reservoir of HDL.[4] Thus, anthropometric and clinical features should be considered when characterizing the population and, at variance to data from Fujii *et al.*, in our study visceral adiposity and fasting glycemia play a role together with HDL-C in predicting risk of HCC in patients with liver fibrosis.

On a different angle, we would lift the veil also on HDL function rather than HDL-C levels *per se*. Indeed, some studies have called into question the hypothesis that the static measurement of HDL-C levels may not perfectly reflect the functional effects of HDL *in vivo* in genetically different populations. For instance, HDL-C levels do not correlate with the cholesterol efflux capacity of macrophages, a measure of cholesterol efflux from peripheral tissues to the liver.[5] Unidirectional flux of cholesterol from macrophages to lipid-free or lipid-poor apolipoproteins, which represents the first step of reverse cholesterol transport, is promoted by transporters belonging to the ATP binding cassette superfamily, namely ABCA1 and ABCG1.[6] Both are transcriptionally regulated by nuclear liver X receptor (LXR)-α/β, which are activated by cholesterol-derived oxysterols. In normal conditions, when the intracellular levels of oxysterols increase, LXR upregulates cholesterol efflux, thus elegantly maintaining its homeostasis. Conversely, when hepatocyte proliferation is required, turning off LXR-transcriptional pathways is crucial to guaranteeing the intracellular cholesterol pool needed for cellular growth.[7] Similarly, in cancer cells, despite the intracellular cholesterol abundance, LXR is downregulated due to the metabolic shift of oxysterol metabolism from anabolic toward catabolic pathways.[8] Thus, from a mechanistic point of view, the reduction of reverse cholesterol transport could be related to increased cancer risk even more than the reduction of HDL-C levels. Moreover, HDL level and function differ between Japanese and Western populations depending on nutritional habits, obesity and metabolic syndrome criteria[9] and on modifications of HDL proteins and lipids that affect HDL functionality.[10]

In conclusion, we agree on the need for further studies to validate the use of HDL in HCC prediction, but evidence about the association of HDL-C and liver fibrosis that also come from Fujii *et al.*'s study confirm our hypothesis on the pathogenic involvement of HDL dysfunction in liver fibrosis and cancer development, at least in individuals with visceral adiposity.

Financial support

A.M. is funded by Italian Association for Cancer Research - AIRC IG 2019 Id 23239.

Conflict of interest

The authors declare no conflict of interest.

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

Authors' contributions

Writing—original draft preparation, L.C. and C.D.M.; writing—review and editing, A.M. All authors have read and agreed to the published version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100783.

Received 14 April 2023; accepted 20 April 2023; ; available online 28 April 2023

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