

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.05.011>.

References

Author names in bold designate shared co-first authorship

[1] **Nachit M, Kwanten WJ**, Thissen J-P, Op de Beeck B, Van Gaal L, Vonghia L, et al. Muscle fat content is strongly associated with NASH: a longitudinal study in patients with morbid obesity. *J Hepatol* 2021;75(2):292–301.

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Reply to: “Intermuscular abdominal fat fraction and metabolic dysfunction-associated fatty liver disease: Does the link already exist in childhood?”

To the Editor:

We thank Dr. Cadenas-Sanchez and colleagues¹ for their interest in our study² and for illustrating that the association between muscle fat and non-alcoholic fatty liver disease (NAFLD)/metabolic dysfunction-associated fatty liver disease (MAFLD) we described in adult patients with morbid obesity also exists in children.¹ Given the increasing prevalence of NAFLD in the pediatric population,³ it is of interest to also explore the muscle compartment in children, as this would open perspectives for new screening and treatment strategies that might be of particular appeal and applicability in this specific population.

The authors report a higher intermuscular abdominal fat fraction (IMAAT) in children with a fatty liver compared to those without fatty liver.¹ The fatty liver has been defined by a liver proton density fat fraction (PDFF) above 5% at MRI. By contrast we are unsure what IMAAT refers to: we assume it might be the ratio of the fat signal to the total fat and water signal (i.e. PDFF) gathered from a region of interest within skeletal muscles at the abdominal level. The term intermuscular might also indicate that IMAAT is the ratio of fat area⁴ (for example,

area of voxels with PDFF >50%) to total fat and muscle area at the abdominal level. It would be good to specify this as well as the muscle bundles used in the quantification so that the study can be continued and contributed to by others.

Thus, children with NAFLD, as early as in the pre/peri-pubertal period, already have a higher muscle fat concentration when compared to those without NAFLD,¹ a finding of particular concern. In adults, we² and others^{5,6} showed that muscle fat, that we called myosteatorosis, increases the risk for hepatic and/or extrahepatic (e.g. cardiovascular) complications. If the same anticipative relationships were true for youth, it would indicate that this is the population on which prevention and treatment efforts should focus. Larger scale population studies that include the measurement of the absolute fat content (a parameter estimated in our study with skeletal muscle fat index²) would be needed to confirm the risk prediction of this strategy.

One must realize that the term “severe NAFLD” does not cover the same reality in the 2 studies: in our study, “severe” pertains to the severity of the necro-inflammatory activity in NAFLD as assessed on liver biopsy. In the pediatric study conducted by Dr. Cadenas-Sanchez¹ “severe MAFLD” refers to severe liver steatosis as defined by MRI PDFF. Such a narrow definition of MAFLD range (only based on fat content) might, at least partly, explain the relatively modest difference in IMAAT described in

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children. Nonetheless, the interesting results reported by Dr. Cadenas-Sanchez and colleagues¹ build a rationale to investigate whether, in children with a fatty liver, a higher muscle fatty infiltration (i.e. fat concentration or absolute fat content) associates with a higher risk of non-alcoholic steatohepatitis (NASH), and of long-term hepatic and extrahepatic complications.

If muscle fat indicates or is correlated with liver lipotoxicity and if a muscle-to-liver axis is involved in NASH pathogenesis, which is currently far from being certain, then reducing muscle fat will become a relevant therapeutic target *per se*.

We would also like to point out that we prefer to avoid confusion in using NAFLD and MAFLD, as they are not simply interchangeable names for this disease.⁷ The proposed MAFLD nomenclature requires a set of criteria to be met, which does not seem to have been applied in the study by Dr. Cadenas-Sanchez *et al.*¹ We would therefore suggest to remain with the NAFLD nomenclature.

Finally, the data reported by Dr. Cadenas-Sanchez and colleagues¹ extend our observations in adults with morbid obesity² to overweight/obese children, and support the screening of muscle fat as a potential marker for the presence and progression of NAFLD that could designate it as a therapeutic target.

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Conflicts of interest

The authors declare that they have no conflict of interest in relation to this work to disclose.

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

Authors' contributions

MN wrote the letter with contribution from all authors.

Supplementary data

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