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

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

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To the Editor

We thank Dr. Cadenas-Sanchez and colleagues[1] for their interest in our study[2] and for illustrating that the association between muscle fat and NAFLD/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 explore the muscle compartment also 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 PDFF above 5% at MRI. By contrast we are unsure of what IMAAT refers to: we assume it might be the ratio of the fat signal to the total fat and water signal (thus the proton density fat fraction; 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 area[4] (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, we[2] and others[5,6] showed that muscle fat, that we called myosteatosis, increases the risk for hepatic and/or extra-hepatic (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 index; SMFI[2]) would be needed to confirm the risk prediction of the strategy.

One must realize that the term “severe NAFLD” does not recover 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-Sanchez[1] “severe MAFLD” coins 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 children. Nonetheless, the interesting results reported by Dr. Cadenas-Sanchez and colleagues[1] 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 higher risk of NASH, and of long-term hepatic and extra-hepatic complications compared to those with a normal muscle fat content.

If indeed muscle fat indicates or is correlated with liver lipotoxicity and if a muscle-to-liver axis is involved in NASH pathogenesis, which to date is far from having been demonstrated, then reducing muscle fat will become a novel relevant therapeutic target *per se* and independently from the overall beneficial effects of physical exercise, such as increased caloric consumption.

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 colleagues[1] extend our observations in adults with morbid obesity[2] to overweight/obese children, and support the screening of muscle fat as a potential marker for the presence of and indicator of progression of NAFLD that could designate it as a therapeutic target.

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Competing Interests

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

Authors' contributions

MN wrote the letter with contribution from all authors.

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