

Rationale of adding muscle volume to muscle fat infiltration in the definition of an adverse muscle composition is unclear



To the Editor:

We read with great interest the recent paper by Linge and colleagues¹ wherein the prevalence and implication of adverse muscle composition (AMC) are evaluated in patients with NAFLD. AMC is defined here as low muscle volume and high muscle fat infiltration (MFI). Muscle data are gained from MRI-derived acquisition²⁻⁴ using automated analyses developed by the authors.^{5,6} The study supports that a poor muscle health status (or AMC) is associated with poor function and a high prevalence of metabolic comorbidities in patients with NAFLD. We fully share the interest in evaluating how the muscle compartment is altered in NAFLD, however we are puzzled by the authors' reading and interpretation of some of the data.

The authors report that fat free muscle volume, whether expressed as a raw value, normalized to height or to a virtual control group, was higher or similar in patients with NAFLD compared to those without NAFLD. Further, the authors found that the proportion of patients with a low handgrip strength was not different between patients with or without NAFLD. Handgrip strength, whose values were regrettably not reported by the authors, is, in the disease context, perhaps the most relevant marker for skeletal muscle function, as it is not directly modulated by obesity-induced mechanical overload. Thus, in the population described, the prevalence of low muscle volume, of low muscle strength, or of sarcopenia (adequately defined by the authors⁷) is lower (or not different) in patients with NAFLD than in those without NAFLD. In the cohort, the degree of MFI was higher in patients with NAFLD compared to patients without, a finding that corroborates data from another large study.⁸ Hence, MFI, rather than low muscle volume or low muscle strength, was associated with NAFLD.

Disconcertingly, the authors suggest that muscle volume should be combined with MFI to delineate an AMC group within the NAFLD population, reported here to be at a higher risk for adverse metabolic and functional outcomes. They suggest that this combination of muscle parameters could "strengthen pre-established sarcopenia guidelines" even though muscle strength (the key determinant of sarcopenia⁷) is discarded from the equation. In our view, there is another reading for the data; hence, we have a proposition for future developments that we would like to share with the authors.

First, in the AMC group (n = 169), sarcopenia was scarce (prevalence of 5.9%, 10/169) whereas high MFI was a defining parameter (prevalence of 100%, 169/169). Besides, muscle volume was higher in patients with NAFLD. Therefore, the higher

proportion of patients with "AMC" in the NAFLD population compared to the non-NAFLD population is preponderantly driven by the greater prevalence of high MFI and not by low muscle volume and/or sarcopenia. A case for considering MFI.

Second, the authors mention that patients with AMC represent an at-risk subgroup (in particular for coronary heart disease events) within NAFLD. The possibility of identifying at-risk patients is highly clinically relevant as cardiovascular events are consistently reported as the first cause of death in patients with NAFLD.⁹ Thus, it would have been very informative to provide data about the relative cardiovascular risk in the AMC or high MFI group in the NAFLD population (1,204 patients) when compared to subjects with AMC or high MFI in the non-NAFLD population (4,122 patients). Indeed, about 10% of the latter vs. 14% of patients with NAFLD have an AMC. Such investigations would have provided insights on whether an AMC or a high MFI *per se* is related to increased cardiovascular risk (as suggested elsewhere¹⁰) and how NAFLD presence truly affects the risk.

Third, we understand that the patients included in the AMC group were systematically excluded from the "low muscle mass only" or "high muscle fat only" group and were never accounted for in analysis comparing a "low muscle mass" or a "high muscle fat" group to the "normal muscle composition" group. Considering that (a) a high MFI or a low muscle strength was far more prevalent (37.8%; 455/1,204 and 6.64%; 80/1,204, respectively) than sarcopenia (1.58%, 19/1,204) in the whole NAFLD population when compared to the non-NAFLD population and (b) the degree of MFI was, by itself, associated with higher cardiovascular and type II diabetes risk (Table S2), we question whether the evaluation of MFI alone, or next to muscle strength (EWGSOP⁷ or percentile-based definition), might better identify patients with adverse metabolic outcome than the proposed AMC criteria based on muscle volume and fat infiltration. Further, this stratified analysis according to MFI and/or muscle strength may help in defining appropriate read-outs, with a non-negligible impact on study designs and recruitment of participating centers: while an MRI-based measure of muscle volume is time consuming or costly, handgrip strength is performed at the bedside using a cheap hand dynamometer and MFI is easily measured by *post hoc* analysis of MRI-derived acquisitions with tools available on any clinically used pictures archiving and communication system (PACS).

Taken together, based on the data presented, the rationale or the scientific value of adding muscle volume to MFI in the definition of an AMC (indicative of an adverse metabolic outcome) appears unclear to us.

Received 13 January 2021; accepted 16 January 2021; ; available online 25 January 2021

Financial support

M.N is supported by the PhD fellowship from FRIA (FNRS, Belgium) [grant number 31618719] and I.L by the Fund for Scientific Medical Research (FNRS Belgium) [grant number T.0141.19].

Conflict of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Author's contributions

Maxime Nachit drafted the manuscript. Yves Horsmans and Isabelle Leclercq have critically revised and finalized the manuscript. All authors have approved the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2021.100235>.

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