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Commentary

Does the benefit of optimal MASH treatment depend on a reduction in myosteatosis?

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ABSTRACT

The muscle-liver axis, well known in cirrhosis, is also important in the multisystem disease known as metabolic dysfunction-associated steatohepatitis (MASH). The convincing results obtained with a triple peroxisome proliferator-activated receptor (PPAR) agonist in this setting confirm this hypothesis, demonstrating a beneficial effect not only on the severity of MASH in terms of steatosis, inflammation and fibrosis, but also in terms of hepatic and muscle insulin sensitivity. The pathophysiology of MASH and mechanism of action of triple PPAR agonist suggest that this may be related to improved lipid management in skeletal muscles and highlights the importance of studying the muscle-adipose tissue-liver axis in the management of MASH.

The muscle-liver axis is well described in cirrhosis, with numerous mechanisms explaining both the muscle consequences in advanced chronic liver disease and potential hepatic abnormalities due to muscle dysfunction [1–3]. This bi-directional muscle-liver connection also operates in cases of insulin resistance [4], as demonstrated by the reference technique, which is the hyperinsulinemic-euglycaemic clamp [5]. The liver-muscle axis is also present in metabolic dysfunction-associated steatotic liver disease (MASLD), which is closely linked to insulin resistance [6], already before cirrhosis occurrence [7]. Interestingly, MASLD patients in non-cirrhotic stages do not present sarcopenia but myosteatosis [8]. This may explain a decrease in muscle density on imaging and an increase in muscle volume [9]. Interestingly, myosteatosis, assessed by muscle density relative to muscle volume, characterises cases of severe MASLD (and metabolic dysfunction-associated steatohepatitis or MASH) [9–11]. MASLD should thus be understood as a multisystem disease, and ideal treatment should consider these connections [4]. The recent results presented in the *Journal of Hepatology* support this evidence, demonstrating that lanifibranor, a triple peroxisome proliferator-activated receptor (PPAR) agonist, which has been shown to be effective in resolving MASH and regressing fibrosis in just 6 months in the NATIVE study [12], reduces not only hepatic steatosis but also hepatic and muscle insulin resistance, using the gold standard clamp technique [13]. To advance in this fascinating field, several avenues could be explored.

Firstly, due to the connection between MASH and myosteatosis and the possible harmful role of skeletal muscle in this situation [14], it would be interesting to know whether lanifibranor induces a modification in the amount of muscle lipids. This could be an easy-to-measure indirect marker in the future. The significant increase in glucose utilisation demonstrated by the lanifibranor treatment [13] could be an indirect sign supporting this hypothesis. Several experiments using PPAR-α, δ or γ agonists alone or in combination also support this action, as demonstrated in a recent review article [15]. However, this has not yet been proven in individuals with MASLD/MASH and myosteatosis treated with lanifibranor [15]. It could also be possible that PPARγ activation increases intramuscular adipocytes, which would increase myocyte insulin sensitivity through a paracrine effect due to an improved lipid management and safer storage [15]. The inclusion of patients undergoing muscle biopsies, magnetic resonance imaging/spectroscopy and intervention would help answer this crucial question, both in terms of pathophysiology and treatment benefit. It is indeed conceivable that the benefit of intervention depends (in part) on the management of muscle lipids [9,15,16].

Secondly, following on from this line of thinking, it seems essential to deepen our understanding of communication between the liver and skeletal muscles [14]. The authors show that the increase in peripheral glucose utilisation during clamp strongly correlates with a decrease in hepatic steatosis [13]. The evaluation of hepatokines, adipokines and myokines would be interesting to advance our understanding of communication between the three organs. For example, fetuin-A and selenoprotein-P, originating from the steatotic liver can lead to insulin resistance in adipose tissue or skeletal muscle [4,17]. Other numerous mediators from the liver to the muscle are possible, such as bile acids, which are linked to both fibrosing MASH and insulin resistance [18] and whose levels are also modulated by PPARα/δ agonists [15]. Conversely, irisin, for example, an exercise-induced myokine is able to reduce hepatic oxidative stress and fibrogenesis but is downregulated in skeletal muscle in the context of MASLD and insulin-resistance [19].

Thirdly, although skeletal muscle uptake is likely responsible for the majority of glucose disappearance with a high-dose insulin infusion protocol, a more accurate assessment of muscle-specific insulin sensitivity in type 2 diabetes and treatment with lanifibranor could be provided by measuring radioisotopes and/or insulin signalling in the muscles during clamping [20].

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Finally, data on muscle function in MASLD patients and its evolution following intervention would also be interesting to collect. It is logical to imagine that muscle insulin resistance and/or myosteatosis have a negative impact on muscle function [14]. The assessment and longitudinal follow-up of parameters such as the well-described liver frailty index in patients with cirrhosis could be evaluated [1]. As for cirrhosis, it will be interesting to determine the muscle parameter most closely linked to the severity of MASLD, the occurrence of complications and the response to interventions [1].

In conclusion, these positive and elegant data on the overall beneficial effect of lanifibranor on peripheral insulin sensitivity open up interesting prospects for the value of adding skeletal muscle to the adipose tissue-liver cross-talk in the management of MASH.

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References

[1] Lanthier N, Stärkel P, Dahlqvist G. Frailty, sarcopenia and mortality in cirrhosis: what is the best assessment, how to interpret the data correctly and what interventions are possible? Clin Res Hepatol Gastroenterol 2021;45:101661. https://doi.org/10.1016/j.clinre.2021.101661.

[2] Henin G, Lanthier N, Dahlqvist G. Pathophysiological changes of the liver-muscle axis in end-stage liver disease: what is the right target? Acta Gastro Enterologica Belgica 2022;85:611–24. https://doi.org/10.51821/85.4.10899.

[3] Goffaux A, Delorme A, Dahlqvist G, Lanthier N. Improving the prognosis before and after liver transplantation: is muscle a game changer? World J Gastroenterol 2022;28:5807–17. https://doi.org/10.3748/wjg.v28.i40.5807.

[4] Stefan N, Schick F, Birkenfeld AL, Häring H-U, White MF. The role of hepatokines in NAFLD. Cell Metab 2023;35:236–52. https://doi.org/10.1016/j.cmet.2023.01.006.

[5] Clarembeau F, Bale G, Lanthier N. Cirrhosis and insulin resistance: current knowledge, pathophysiological mechanisms, complications and potential treatments. Clin Sci 2020;134:2117–35. https://doi.org/10.1042/CS20200022.

[6] Jain P, Jain A, Deshmukh R, Samal P, Satapathy T, Ajazuddin. Metabolic dysfunction-associated steatotic liver disease (MASLD): exploring systemic impacts and innovative therapies. Clin Res Hepatol Gastroenterol 2025;49:102584. https://doi.org/10.1016/j.clinre.2025.102584.

[7] Bale G, Clarembeau F, Stärkel P, Dahlqvist G, Horsmans Y, Lanthier N. Patients with chronic liver diseases are at risk for diabetes even before development of cirrhosis. Clin Res Hepatol Gastroenterol 2024;48:102428. https://doi.org/10.1016/j.clinre.2024.102428.

[8] De Munck TJI, Verhaegh P, Lodewick T, Bakers F, Jonkers D, Masclee AAM, et al. Myosteatosis in nonalcoholic fatty liver disease: an exploratory study. Clin Res Hepatol Gastroenterol 2020. https://doi.org/10.1016/j.clinre.2020.06.021.

[9] Nachit M, Lanthier N, Rodriguez J, Neyrinck AM, Cani PD, Bindels LB, et al. A dynamic association between myosteatosis and liver stiffness: results from a prospective interventional study in obese patients. JHEP Reports 2021;3:100323. https://doi.org/10.1016/j.jhepr.2021.100323.

[10] Lanthier N, Rodriguez J, Nachit M, Hiel S, Trefois P, Neyrinck AM, et al. Microbiota analysis and transient elastography reveal new extra-hepatic components of liver steatosis and fibrosis in obese patients. Sci Rep 2021;11:659. https://doi.org/10.1038/s41598-020-79718-9.

[11] 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;75:292–301. https://doi.org/10.1016/j.jhep.2021.02.037.

[12] Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. New Engl J Med 2021;385:1547–58. https://doi.org/10.1056/nejmoa2036205.

[13] Barb D, Kalavalapalli S, Godinez Leiva E, Bril F, Huot-Marchand P, Dzen L, et al. Pan-PPAR agonist lanifibranor improves insulin resistance and hepatic steatosis in patients with T2D and MASLD. J Hepatol 2025;82:979–91. https://doi.org/10.1016/j.jhep.2024.12.045.

[14] Henin G, Loumaye A, Leclercq IA, Lanthier N. Myosteatosis: diagnosis, pathophysiology and consequences in metabolic dysfunction-associated steatotic liver disease. JHEP Reports 2024;6:100963. https://doi.org/10.1016/j.jhepr.2023.100963.

[15] Boliaki N, Henin G, Bale G, Lanthier N. Impact of Peroxisome Proliferator-Activated Receptor Agonists on Myosteatosis in the Context of Metabolic Dysfunction-Associated Steatotic Liver Disease. Discov Med 2024;36:1139. https://doi.org/10.24976/Discov.Med.202436185.104.

[16] Henin G, Loumaye A, Deldicque L, Leclercq IA, Lanthier N. Unlocking liver health: can tackling myosteatosis spark remission in metabolic dysfunction-associated steatotic liver disease? Liver Int 2024;44:1781–96. https://doi.org/10.1111/liv.15938.

[17] Lanthier N, Lebrun V, Molendi-Coste O, van Rooijen N, Leclercq IA. Liver Fetuin-A at Initiation of Insulin Resistance. Metabolites 2022;12:1023. https://doi.org/10.3390/metabo12111023.

[18] Grzych G, Chávez-Talavera O, Descat A, Thuillier D, Verrijken A, Kouach M, et al. NASH-related increases in plasma bile acid levels depend on insulin resistance. JHEP Reports 2021;3:100222. https://doi.org/10.1016/j.jhepr.2020.100222.

[19] Marjot T, Armstrong MJ, Stine JG. Skeletal muscle and MASLD: mechanistic and clinical insights. Hepatol Commun 2025;9. https://doi.org/10.1097/HC9.0000000000000711.

[20] Koh H-CE, van Vliet S, Meyer GA, Laforest R, Gropler RJ, Klein S, et al. Heterogeneity in insulin-stimulated glucose uptake among different muscle groups in healthy lean people and people with obesity. Diabetologia 2021;64:1158–68. https://doi.org/10.1007/s00125-021-05383-w.

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