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Reply

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We appreciate the summary and interpretation of the findings of our NASHFit Trial by Zanetto et al.[1] This was the first study investigating how exercise can mitigate thrombotic risk in patients with NASH. We found that the plasma level of plasminogen activator inhibitor (PAI)-1 was significantly decreased following 20 weeks of exercise training, independent of obesity or body composition. These findings are important because patients with NASH have increased rates of thromboembolism.[2] Decreasing PAI-1, which is abnormal and leads to impaired fibrinolysis (clot breakdown) in NASH, would be expected to lessen thromboembolism and its subsequent morbidity and mortality.

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AUTHOR CONTRIBUTIONS

All authors contributed in the following manner and (1) drafted the article or revised it critically for important intellectual content and (2) provided final approval of the version to be published.

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PAI-1 is an established biomarker of thrombotic complications across multiple populations, including those with metabolic disease. In patients with NASH, there is a large body of evidence demonstrating increased PAI-1 level in a dose-dependent fashion across all disease stages.[3] We previously demonstrated that PAI-1 level was much greater in liver transplant candidates with NASH cirrhosis and that PAI-1 level normalizes within 1 week following transplantation.[4] However, our study was underpowered to detect an association between PAI-1 and thromboembolism. To date, we are unaware of any prospective studies linking PAI-1 to thrombotic events exclusively in patients with NASH.

In this letter, Zanetto et al. provide new evidence to support PAI-1 as a biomarker of thromboembolism in NASH. In their *post hoc* analysis of 26 patients with NASH cirrhosis, PAI-1 level was significantly greater in the 5 patients who developed venous thromboembolism, independent of other components of the fibrinolytic system. Although interpretation of these results needs to be performed cautiously given the relatively small sample size consisting largely of male patients with decompensated cirrhosis, the findings are nonetheless promising and provide additional evidence linking impaired fibrinolysis to thrombotic events in NASH. We look to future prospective studies to validate these findings and confirm that PAI-1 remains a relevant thrombotic biomarker in patients with NASH across all stages of disease.

REFERENCES

1. Stine JG, Schreibman IR, Faust AJ, Dahmus J, Stern B, Soriano C, et al. NASHFit: a randomized controlled trial of an exercise training program to reduce clotting risk in patients with NASH. Hepatology. 2022;76:172–85. [PubMed: 34890063]
2. Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to non-alcoholic steatohepatitis (NASH). Liver Transpl. 2015;21:1016–21. [PubMed: 25845711]
3. Targher G, Bertolini L, Rodella S, Lippi G, Franchini M, Zoppini G, et al. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. Obesity (Silver Spring). 2008;16:1394–9. [PubMed: 18369343]
4. Rivas G, Hummer-Bair B, Bezinover D, Kadry Z, Stine J. Plasminogen activator inhibitor is significantly elevated in liver transplant recipients with decompensated NASH cirrhosis. BMJ Open Gastroenterol. 2021;8:e000683.