Journal of Clinical and Translational Hepatology **2021** vol. 9(4) | 454–455
DOI: 10.14218/JCTH.2021.00236

Editorial

Serum Resistin as a Biomarker in Nonalcoholic Fatty Liver Disease: Is This a Road to be Taken?

Dimitrios Patoulias*

Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, General Hospital "Hippokration", Thessaloniki, Greece

Received: 20 June 2021 | **Revised:** 5 July 2021 | **Accepted:** 12 July 2021 | **Published:** 3 August 2021

Citation of this article: Patoulias D. Serum resistin as a biomarker in nonalcoholic fatty liver disease: is this a road to be taken? J Clin Transl Hepatol 2021;9(4):454–455. doi: 10.14218/JCTH.2021.00236.

Nonalcoholic fatty liver disease (NAFLD), which encompasses a broad spectrum ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), constitutes a global nightmare, since it affects up to one-fourth of people worldwide, representing a major cause of cirrhosis and hepatocellular carcinoma.[1] Besides the fact that NAFLD is usually thought to be closely related to obesity, almost 40% of affected individuals are classified as nonobese and 20% as lean, all of whom consequently suffer from excessive morbidity and mortality as well.[2] NAFLD is interconnected with significant comorbidities, namely atherosclerotic cardiovascular disease (although it is still a controversial area of knowledge), chronic kidney disease, type 2 diabetes mellitus (T2DM), atrial fibrillation, and obstructive sleep apnea.[3–8] Therefore, there is an urgent need for biomarkers that could contribute to the identification and risk stratification of subjects with NAFLD, especially those with or at high risk for major comorbidities, and their response to therapeutic management.

Recently, another disease profile has been proposed to replace the existing one for NAFLD, termed as "metabolic dysfunction-associated fatty liver disease" (MAFLD) with diagnosis being based upon histological criteria (liver biopsy), imaging or circulating biomarker evidence of fat accumulation in the liver (hepatic steatosis) in addition to one of the following three criteria, namely overweight/obesity, presence of T2DM, or evidence of metabolic dysregulation.[9] This definition, despite initial doubts, may be of better clinical utility, as demonstrated in recent cohort studies.[10]

In the present issue of *Journal of Clinical and Translational Hepatology*, Han and colleagues[11] performed a thorough and methodologically rigorous meta-analysis assessing the potential applicability of serum resistin, a pro-inflammatory adipokine, as a biomarker of NAFLD at its entire spectrum. The authors initially demonstrated that subjects with NAFLD have significantly higher serum resistin levels compared to controls [standardized mean difference (SMD) = 0.522, 95% confidence interval (CI): 0.004 to 1.040, I^2=95.9%] and subjects with NASH have lower serum resistin levels than the healthy controls (SMD = −0.44, 95% CI: −0.83 to −0.55, I^2=74.5%), while no significant difference was identified for patients with NAFL compared to controls and patients with NAFL compared to those with NASH. Based on the contradictory results, Han *et al*.[11] performed a meticulous sensitivity analysis, documenting that patients with NASH have lower resistin levels compared to healthy controls, whereas no significant difference between NAFL patients versus controls and NAFL versus NASH patients exists. Additionally, their thorough meta-regression analysis failed to identify any significant source of the high observed heterogeneity for the generated results. The high number of included studies and the extensive subgroup, sensitivity and meta-regression analyses attribute further power to the generated results, despite the significant heterogeneity.

As the authors state, in interpreting the retrieved results, "*resistin levels seem to rise with the progression of NAFLD, from healthy to NAFL, but decline when NAFL progresses to NASH*". The question that arises is then "*who and when should be monitored*"? According to these results, it seems that resistin may be inadequate to serve as a marker for the distinguishment of a patient with NAFLD from the general population but may be useful for fibrosis risk stratification of a patient with an established diagnosis of NAFLD, since lower levels might indicate more severe disease. Its association with liver tumorigenesis (as shown in hepatitis C virus-infected patients with liver cirrhosis) could enhance this diagnostic strategy, although further data is required.[12] In addition, circulating resistin might be useful for the early identification of patients with some form of NAFLD at high risk for developing other co-morbidities, such as cardiovascular disease and renal impairment.[13,14]

To sum up, the meta-analysis by Han *et al*.[11] provides new, significant insights into the role of circulating resistin as a biomarker in NAFLD. According to current knowledge, it seems that this adipokine could be useful for monitoring of liver fibrosis among NAFLD patients, while it might have a role in the early detection of NAFLD-related comorbidities. However, it seems that further research in the field is still required to determine its exact role in risk stratification of affected individuals. Cost-effectiveness analyses are required, in order to establish resistin as a biomarker of choice in NAFLD.

Abbreviations: CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SDM, standardized mean difference; T2DM, type 2 diabetes mellitus.

***Correspondence to:** Dimitrios Patoulias, Second Propedeutic Department of Internal Medicine, General Hospital "Hippokration", Konstantinoupoleos 49, Thessaloniki 54642, Greece. ORCID: https://orcid.org/0000-0002-6899-684X. Tel: +30-6946900777, Fax: +30-2310225083, E-mail: dipatoulias@gmail.com

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

References

[1] Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet 2021;397(10290):2212–2224. doi:10.1016/S0140-6736(20)32511-3.
[2] Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, *et al*. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5(8):739–752. doi:10.1016/S2468-1253(20)30077-7.
[3] Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J Hepatol 2016;65(3):589–600. doi:10.1016/j.jhep.2016.05.013.
[4] Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, *et al*. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. BMJ 2019;367:l5367. doi:10.1136/bmj.l5367.
[5] Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Schattenberg JM, *et al*. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. Gut 2020:gutjnl-2020-323082. doi:10.1136/gutjnl-2020-323082.
[6] Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes Care 2018;41(2):372–382. doi:10.2337/dc17-1902.
[7] Mantovani A, Dauriz M, Sandri D, Bonapace S, Zoppini G, Tilg H, *et al*. Association between non-alcoholic fatty liver disease and risk of atrial fibrillation in adult individuals: An updated meta-analysis. Liver Int 2019;39(4):758–769. doi:10.1111/liv.14044.
[8] Jullian-Desayes I, Trzepizur W, Boursier J, Joyeux-Faure M, Bailly S, Benmerad M, *et al*. Obstructive sleep apnea, chronic obstructive pulmonary disease and NAFLD: an individual participant data meta-analysis. Sleep Med 2021;77:357–364. doi:10.1016/j.sleep.2020.04.004.
[9] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–209. doi:10.1016/j.jhep.2020.03.039.
[10] Niriella MA, Ediriweera DS, Kasturiratne A, De Silva ST, Dassanayaka AS, De Silva AP, *et al*. Outcomes of NAFLD and MAFLD: results from a community-based, prospective cohort study. PLoS One 2021;16:e0245762. doi:10.1371/journal.pone.0245762.
[11] Han D, Chen J, Liu S, Zhang Z, Zhao Z, Jin W, *et al*. Serum resistin levels in adult patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. J Clin Transl Hepatol 2021;9(4):484–493. doi:10.14218/JCTH.2021.00018.
[12] Elsayed EY, Mosalam NA, Mohamed NR. Resistin and insulin resistance: a link between inflammation and hepatocarcinogenesis. Asian Pac J Cancer Prev 2015;16(16):7139–7142. doi:10.7314/apjcp.2015.16.16.7139.
[13] Bonito B, Silva AP, Rato F, Santos N, Neves PL. Resistin as a predictor of cardiovascular hospital admissions and renal deterioration in diabetic patients with chronic kidney disease. J Diabetes Complications 2019;33(11):107422. doi:10.1016/j.jdiacomp.2019.107422.
[14] Fontana A, Spadaro S, Copetti M, Spoto B, Salvemini L, Pizzini P, *et al*. Association between resistin levels and all-cause and cardiovascular mortality: a new study and a systematic review and meta-analysis. PLoS One 2015;10(3):e0120419. doi:10.1371/journal.pone.0120419.