1st GLOBAL LIVER HEALTH FORUM

NAFLD and metabolic comorbidities – current understanding and perspectives

Prof Jörn M. Schattenberg

Director of the Metabolic Liver Research Program,
University Medical Center Mainz, Germany.

Flash for webinar (~20 mins)

SANOFI

NAFLD and metabolic comorbidities – current understanding and perspectives

Risk stratification

The development and progression of NAFLD is associated with a number of risk factors, including age, gender, BMI, ethnicity and comorbidities (e.g. type 2 diabetes, hypercholesterolemia and hypertension).[1] Personalization through clinical risk stratification is possible, for example with diabetes as a predictor of advanced fibrosis.[2]

In particular, there is a strong relationship between metabolic comorbidities and NAFLD severity – for patients with mild NAFLD, the odds ratio of having metabolic burden is 3.64 (95% CI: 1.5–8.8) vs no NAFLD; and for patients with moderate-to-severe NAFLD, the odds ratio of having metabolic burden is 9.4 (95% CI: 3.5–25.0) vs no NAFLD.[3] The liver interacts with other organs in the context of metabolically-ill patients and data from population-based analyses in Germany suggest that NAFLD also contributes to extrahepatic diseases.[4]

Disease progression and importance of early diagnosis

NAFLD is a multifactorial, progressive disease and, as such, early diagnosis will better target treatment to those who are most likely to benefit from intervention. A meta-analysis of 13 studies including 4428 patients with liver histology, 65% of whom had NASH, found that more advanced fibrosis was associated with a higher risk of all-cause mortality.[5]

The pathogenesis of hepatic steatosis involves disruption of metabolic pathways – the DNL pathway is promoted and β–oxidation is impaired.[6,7] Further to this, there is a correlation between steatosis progression and metabolic comorbidities. Steatosis, as an early change, may be a risk factor not only for NAFLD progression but also for other cardiometabolic disorders.[3]

Screening and diagnostics

According to clinical guidance, screening by ultrasound is recommended in high-risk groups.[8] Since transaminases are not elevated in 80% of NAFLD patients,[9] generally enzyme levels are not recommended as the screening modality as they do not reflect steatosis and NAFLD severity/stage.[10] Importantly, recent guidance from the ADA advises that people with T2DM or pre-diabetes and elevated liver enzymes or fatty liver on ultrasound should be evaluated for the presence of NASH and liver fibrosis.[11]

ADA: American Diabetes Association; **AST:** aspartate transaminase; **AUROC:** area under the receiver operating characteristic curve; **BMI:** body mass index; **CAP:** controlled attenuation parameter; **CI:** confidence interval; **DNL:** *de novo* lipogenesis; **EASL:** European Association for the Study of the Liver; **LSM:** liver stiffness measurement; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes.

NAFLD and metabolic comorbidities – current understanding and perspectives

Further to the ADA recommendations, EASL guidelines provide a flow-chart for diagnosis, indicating that metabolic work-up must carefully assess all components of the metabolic syndrome.[12] In addition, they also advise that the presence of obesity/T2DM or raised liver enzymes in patients with metabolic risk factors should prompt non-invasive screening to predict steatosis, NASH and fibrosis.[12]

While ultrasound represents the first-line imaging technique for diagnosing steatosis,[13] additional non-invasive techniques are available, such as the Fatty liver index (FLI); NAFLD liver fat score (NAFLD–LFS) and hepatic steatosis index (HIS).[14] The FibroScan-AST (FAST) score also provides an efficient way of non-invasively identifying patients at risk of NASH progression.[15] This is a predictive model combining LSM, CAP and AST, and in a prospective study its predictive performance indicated an AUROC of 0.80 (95% CI: 0.76–0.85) across the validation cohorts tested (N=350).[15]

In the future, artificial intelligence may also be used for diagnosis NAFLD/NASH, as it has demonstrated capability of identifying 14 parameters which discriminate NASH from non-NASH.[16]

References

1. Younossi ZM, *et al.* Epidemiology of chronic liver diseases in the USA in the past three decades. Gut. 2020;69:564–8.
2. Wong RJ, *et al.* Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross-sectional analysis of 2011-2014 National Health and Nutrition Examination Survey. Aliment Pharmacol Ther. 2017;46:974–80.
3. Yang KC, *et al.* Association of Non-alcoholic Fatty Liver Disease with Metabolic Syndrome Independently of Central Obesity and Insulin Resistance. Sci Rep. 2016;6:27034.
4. Labenz C, *et al.* Impact of NAFLD on the Incidence of Cardiovascular Diseases in a Primary Care Population in Germany. Dig Dis Sci. 2020;65:2112–19.
5. Taylor RS, *et al.* Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;158:1611–25.
6. Hodson L & Gunn PJ. The regulation of hepatic fatty acid synthesis and partitioning: the effect of nutritional state. Nat Rev Endocrinol. 2019;15:689–700.
7. Postic C & Girard J. Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice. J Clin Invest. 2008;118:829–38.
8. Leoni S, *et al.* Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis. World J Gastroenterol. 2018;24:3361–73.
9. Dyson JK, *et al.* Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. Frontline Gastroenterology. 2014;5:211–8.
10. Kotronen A & Yki-Järvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol. 2008;28:27–38.
11. ADA. Diabetes Care 2019;42(Suppl 1):S34–S45.
12. EASL-EASD CPG NAFLD. J Hepatol 2016;64:1388–402.
13. Byrne CD, *et al.* Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. BMJ 2018;362:k2734.
14. Bugianesi E, *et al.* How to diagnose NAFLD in 2016. J Hepatol. 2016;65:643–644.
15. Newsome PN, *et al.* FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;5:362–73.
16. Schattenberg JM, *et al.* AASLD 2019.

ADA: American Diabetes Association; **AST:** aspartate transaminase; **AUROC:** area under the receiver operating characteristic curve; **BMI:** body mass index; **CAP:** controlled attenuation parameter; **CI:** confidence interval; **DNL:** *de novo* lipogenesis; **EASL:** European Association for the Study of the Liver; **LSM:** liver stiffness measurement; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **T2DM:** type 2 diabetes.

NAFLD and metabolic comorbidities – current understanding and perspectives

Learning objectives:

Explore the relationship between metabolic comorbidities, such as type 2 diabetes and obesity, and NAFLD severity.

Understand the importance of early diagnosis of NAFLD and consider how this may impact patient outcomes.

Review the available diagnostic techniques in screening and staging of NAFLD/NASH.

Main take aways:

- NAFLD severity is linked to metabolic comorbidities – diabetes and high BMI.
- Early-stage NAFLD exhibits lower mortality and morbidity versus advanced disease.
- Early diagnosis could allow for improved disease management and outcomes for patients.
- Screening is necessary for high-risk NAFLD patients, including those with diabetes or obesity.
- Non-invasive tests are increasingly available for NAFLD/NASH.

SANOFI

MAT-GLB-2003464