2nd GLOBAL LIVER HEALTH FORUM

PUTTING MAFLD INTO PERSPECTIVE – LIVER-DIRECTED HEPATOPROTECTIVE TREATMENT OPTIONS

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NAFLD and metabolic syndrome (MetS)

NAFLD is closely associated with features of MetS such as insulin resistance, hyperglycemia, obesity and dyslipidemia.[1,2] Patients with obesity, raised fasting glucose levels, T2DM or other metabolic abnormalities have an increased risk of advanced fibrosis compared with those without metabolic abnormalities.[1] Because advanced fibrosis is associated with liver-related events, metabolic abnormalities have the potential to predict a poorer long-term prognosis in patients with NAFLD.[3,4] Therefore, metabolic disorders should be considered when screening for liver fibrosis. Current non-invasive diagnostic tests need to be improved in terms of their performance, accessibility and cost-effectiveness.

The role of metabolic disorders in screening for liver fibrosis

Metabolic disorders combined with non-invasive tests to screen for advanced fibrosis in NAFLD have been assessed in the TOWARDS1 study: an observational, cross-sectional registry study conducted across 14 sites in China.[4] This study enrolled 246 adult patients with biopsy-proven NAFLD. Demographic and anthropometric characteristics, medical history and metabolic disorders were collected at enrolment. Patients with more metabolic disorders had significantly more severe fibrosis than patients with fewer metabolic disorders (P=0.017). Reduced HDL-C (P=0.049) and raised fasting glucose (P<0.001) were significantly associated with advanced fibrosis. Combining the new diagnostic tool, MetDis (reduced HDL-C and raised fasting glucose), with the standard non-invasive test FIB-4, reduced the number of patients requiring liver biopsy compared with FIB-4 alone (36% to 17%, P<0.001).[4]

Because of the strong association between NAFLD and metabolic dysfunction, it has been proposed that the name 'metabolic-associated fatty liver disease (MAFLD)' is a more appropriate term than NAFLD.[5] Some research suggests that the MAFLD criteria are more effective at identifying patients at risk of fibrosis and metabolic dysfunction than NAFLD.[6,7] However, comparisons of NAFLD and MAFLD terminology have been based on non-invasive indicators of fibrosis rather than comparing liver pathology and its relevance to MAFLD diagnostic criteria.

Metabolic components in predicting the severity of NAFLD

In the TOWARDS1 study, most patients (97.2%) met the criteria for MAFLD.[5] The positive diagnostic criteria of MAFLD include overweight/obesity, presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation, regardless of alcohol consumption or other concomitant liver diseases.[5] The presence of MetS was associated with a greater severity of steatohepatitis and liver fibrosis. HOMA-IR ≥2.5 was the most significant risk factor for NASH (P=0.001) and liver fibrosis (P=0.004) indicating that patients' insulin resistance status may predict the progression of liver fibrosis and NASH.[5]

In a *post-hoc* analysis, CHB patients with NASH had higher BMI, higher proportion of overweight, and higher steatosis score compared with those without NASH (all P<0.001).[8]

Patients with baseline BMI ≥23 kg/m2 (overweight in the Asian population) and weight gain during follow-up were less likely to experience improvement or resolution of NASH than those with baseline BMI <23 kg/m^2 and no weight gain.[8]

Current treatment guidelines and the potential role of EPLs

The Chinese guidelines on the treatment of NAFLD recommend lifestyle modifications including diet, weight loss and physical activity as first-line management to reduce serum aminotransferase levels and improve hepatic steatosis/steatohepatitis.[9] Following this, pharmacotherapy is used to improve insulin resistance and glucose/lipid metabolism.[9] The use of hepatoprotective agents, including PPC, vitamin E silymarin, adenosylmethionine, and reduced glutathione is optional as adjunct therapy in patients with biopsy-confirmed NASH, NAFLD with abnormal liver functions, significant liver injury, or signs of advanced hepatic fibrosis.[10,11]

EPL given as adjunctive therapy to metformin or SOC in patients with NAFLD and T2DM have been associated with improved clinical outcomes compared with T2DM-specific treatment alone.[11–13] In a study of patients with NAFLD and T2DM,[11] a significantly greater overall response rate was observed with EPL plus metformin compared with metformin alone (78.4% vs. 54.1%, P<0.05). EPL therapy has also resulted in improvements in clinical outcomes for patients with NAFLD and hyperlipidemia or obesity.[14–16] In a study of patients with NAFLD and obesity, polyenyl phosphatidylcholine (PPC) plus sibutramine resulted in a significant reduction in steatosis from baseline and led to significant improvement in ultrasound results in 92.0% of patients. PPC plus sibutramine also resulted in slower fibrosis progression than sibutramine alone (P<0.05).[17]

References

1. Jinjuvadia R, et al. J Clin Gastroenterol 2018;51(2):160–66
2. Vernon G, et al. Aliment Pharmacol Ther 2011;34(3):274–85
3. Dulai PS, et al. Hepatol 2017;65(5):1557–65
4. Shi YW, et al. J Clin Transl Hepatol 2021; doi:10.14218/JCTH.2021.0005
5. Yang RX, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.002
6. Lin S, et al. Lv Int 2020;40(9):2082–89
7. Yamamura S, et al. Liv Int 2020;40(12):3018–30
8. Chang XJ, et al. Hepatobiliary Pancreat Dis Int 2021; doi:10.1016/j.hbpd.2021.06.009
9. Gao X, et al. J Diabetes 2013;406–15
10. Fan JG, et al. J Dig Dis 2018;1–11
11. Li Z. Inner Mongol Journal of Traditional Chinese Medicine 2013;31:10–1
12. Sun C, et al. Clinical Focus 2008;23:1272–3
13. Wu CY. Pract Clin Med 2015;16:3–5
14. Maev IV, et al. BMJ Open Gastroenterol 2019;6:e000307;
15. Maev IV, et al. BMJ Open Gastroenterol 2020;7:e000368;
16. Maev IV, et al. BM J Open Gastroenterol 2020;7:e000341;
17. Sas E, et al. Gut 2012;61:A216–A7

BMI, body mass index; CHB, chronic hepatitis B; EPL, essential phospholipids; FIB-4, fibrosis-4 index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; MetDis, metabolic disorders; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic-associated fatty liver disease; PC, polyenyl phosphatidylcholine; SOC, standard-of-care; T2DM, type 2 diabetes mellitus.

Learning objectives:

- Understand NAFLD is closely associated with features of MetS
- Gain an insight into the role of metabolic disorders in screening for liver fibrosis
- Explore the association between metabolic components and the pathological severity of NAFLD
- Become familiar with the current treatment guidelines and the potential role of EPL

Main takeaways:

- Combining the new diagnostic tool, MetDis (reduced HDL-C and raised fasting glucose) with FIB-4 may provide an accurate, non-invasive method for diagnosis of advanced fibrosis
- The presence of MetS has been associated with a greater severity of steatohepatitis and liver fibrosis in patients with NAFLD
- Insulin resistance status may be more important in the progression of NAFLD than obesity and history of diabetes
- Current guidelines recommend lifestyle modifications as first-line treatment for NAFLD, followed by anti-obesity medications, medications to improve insulin resistance and metabolic status, and hepatoprotective agents

EPL, essential phospholipids; HDL-C, high-density lipoprotein cholesterol; MetDis, metabolic disorders; MetS, metabolic syndrome NAFLD, non-alcoholic fatty liver disease.

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