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THE IMPORTANCE OF FAST IDENTIFICATION AND UNDERSTANDING DISEASE PROGRESSION – KEY NOTES FOR NAFLD MANAGEMENT

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Natural history of NAFLD (also known as MAFLD)

NAFLD encompasses a histological spectrum ranging from NAFL, characterized by steatosis with minimal or no inflammation, to NASH, in which lobular inflammation and hepatocellular ballooning are present, with or without fibrosis.[1] The timeframe for progression from NAFLD to NASH and cirrhosis varies; approximately one-quarter of patients progress to NASH within 3 years, and almost half of patients progress within 6 years.[2] Emerging data suggests that fibrosis, rather than NASH *per se*, is the most important histological predictor of liver and non-liver related death in patients with NAFLD.[3]

Predictive factors for NAFLD progression to fibrosis

There are multiple predictive factors for the risk of progression to fibrosis. Increasing age, BMI, and degree of liver inflammation are associated with progression to NASH and advanced fibrosis, and the emergence of T2DM parallels fibrosis progression.[2,4,5] Men and post-menopausal women have a higher risk of fibrosis than pre-menopausal women.[2,4] Polymorphisms in the PNPLA3 and TM6SF2 genes, hepatic iron deposits, and elevated AST/ALT ratio are also implicated in NAFLD progression.[2,5]

Identification of patients with NAFLD at risk for NASH

Several tools are available to stratify patients by risk of advanced fibrosis, including the NAFLD Fibrosis Score and Fibrosis-4 Index.[6–8] Both of these tools incorporate data on age, AST/ALT ratio and platelet count, and the NAFLD Fibrosis Score also factors in BMI, albumin, and the presence of impaired fasting glucose or diabetes.[6–8]

Whilst progression risk can be determined via liver biopsy, this is expensive, invasive, and prone to sampling and reader variability, and is therefore not appropriate for many patients.[1] However, transient elastography can be used in an ambulatory setting to obtain continuous attenuation parameters. Vibration-controlled transient elastography with FibroScan® can be used to detect advanced fibrosis, predict the risk of decompensation and complications, and correlates well with portal pressure.[9,10]

MR imaging, either by spectroscopy or by proton density fat fraction, is another non-invasive modality for quantifying hepatic steatosis, and is being widely used in NAFLD clinical trials.[11]

The progression of NASH: key factors in disease management

At present, the management of NAFLD is largely based on patient lifestyle modifications. A long-term reduction in calorie intake is associated with mobilization of liver fat and improvement in cardiovascular risk, and the Mediterranean diet has been shown to improve steatosis (albeit long-term, prospective data are lacking).[1] Additional favourable lifestyle changes include the avoidance of added sugar and heavy alcohol consumption, and the consumption of ≥2 cups of caffeinated coffee daily.[12,13]

Weight loss is a key part of NAFLD management; a meta-analysis of eight randomized trials found that participants who lost ≥5% of their bodyweight experienced improvement in steatosis. Additionally, a 12-month prospective trial found a dose-response relationship between the amount of weight lost and the degree of improvement in histopathologic parameters, although only a ≥5% loss resulted in stabilization or improvement of fibrosis in 94% of patients.[11]

Exercise alone may prevent or reduce steatosis, but its ability to improve other aspects of liver histology have yet to be determined.[11] Bariatric surgery can be considered in individuals with NAFLD or NASH who otherwise meet the eligibly criteria, but bariatric surgery is not indicated solely for the treatment of NAFLD/NASH.[11]

EPL in patients with NAFLD, with or without relevant comorbidities

The efficacy of EPL as add-on treatment to standard of care in patients with NAFLD, with or without T2DM and/or hyperlipidemia, has been assessed in a prospective, randomized, open-label study.[14] Patients received EPL 1800 mg three-times daily for 24 weeks, followed by 900 mg three-times daily for 48 weeks. In patients with lone NAFLD, NALFD + T2DM, and NAFLD + hyperlipidemia, statistically significant improvements in clinical signs and symptoms ($p<0.01$) and transaminases ($p<0.01$) occurred.[14] In lone NAFLD, NAFLD + T2DM, and NAFLD + hyperlipidemia, respectively, appreciable improvements upon ultrasound examination were observed in 29.2%, 23.4%, and 20.2% of patients; improvement in liver stiffness upon elastography was observed in 14.2%, 26.1%, and 20.2% of patients, respectively.[14]

A systematic review and network meta-analysis of four studies reporting results for the efficacy of EPL in patients with NAFLD and obesity or T2DM found that there was a significantly greater reduction in ALT, triglycerides and cholesterol with EPLs plus antidiabetic therapy compared with antidiabetic therapy alone.[15]

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ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; EPL, essential phospholipids; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic-associated fatty liver disease; MR, magnetic resonance; PNPLA3, patatin-like phospholipase domain-containing protein; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2

Learning objectives:

- Understand the natural history of NAFLD (MAFLD)
- Gain an insight into the identification of patients with NAFLD at risk for NASH
- Explore the progression of NASH and the key factors in disease management
- Become familiar with the current treatment landscape

Main takeaways:

- The management of patients with NASH comprises two key challenges:
  - The stratification of patients with a high risk of liver-related complications
  - The identification of predictive factors for progressive fibrosis (the most important parameter associated with outcomes in patients with NAFLD)
- Patients with NAFLD who are at risk of NASH, and therefore require follow-up, may be rapidly identified using non-invasive tests
- There is a growing body of evidence supporting the beneficial role of EPL in the multifaceted management of patients with NAFLD and metabolic comorbidities

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic-associated fatty liver disease

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