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CARDIOVASCULAR AND METABOLIC RISKS OF MAFLD: IMPORTANT CONSIDERATIONS FOR CLINICAL PRACTICE

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MAFLD is a multi-systemic disease that increases the risk of T2DM and CVD

MAFLD is a multi-system disorder.[1] Diet-induced obesity drives metabolic stress, insulin resistance in adipose tissue and systemic inflammation and fibrosis, increasing the risk of T2DM and metabolic syndrome.[1] MAFLD can present with a wide spectrum of other extrahepatic diseases such as chronic kidney disease, extrahepatic malignancies and cognitive disorders.[2] The most advanced stage of MAFLD, NASH, has systemic effects throughout the body and is associated with the greatest risk of cardiometabolic comorbidities.[1,2] Indeed, the prevalence of T2DM among the general population of the USA is 14%, and increases to 22.5% among those with non-NASH MAFLD and 43.6% in those with NASH.[3]

Multiple studies confirm the relationship between MAFLD and CVD

MAFLD has been shown to increase the risk of subclinical atherosclerosis, CAD and CV events. In a meta-analysis of 14 studies, including 2,932 patients, there was a higher prevalence of CIMT (35.1% vs 21.8%; p<0.0001) and CAD (80.4% vs 60.7%; p<0.0001) among patients with MAFLD versus those without, respectively.[4] In addition, a prospective study demonstrated a higher prevalence of CV events among patients with MAFLD versus those without (19% vs 10%, respectively; p=0.007), with one of the strongest predictors of CV events being hepatic steatosis (HR=1.99; 95% CI: 1.01–3.94).[5]

MAFLD/NASH have also been associated with an increased risk of mortality. In a cohort study to re-evaluate survival and cause of death in patients with MAFLD, survival of those with NASH was reduced versus the general population, with these patients more often dying from CV and liver-related causes (p=0.04 for both).[6] Similarly, another population-based cohort study revealed a higher rate of mortality in patients with MAFLD versus those without MAFLD, with the three main causes of death cited as cancers, CV events, cirrhosis and HCC.[7] These findings have been corroborated by a multicentre, retrospective study of 10,071 patients with and without MAFLD in China.[8] Those with MAFLD had higher proportions of death due to underlying CVD and liver-related diseases than the general population, and these proportions positively correlated with degree of steatosis.[8]

Furthermore, the severity of liver fibrosis correlates with CV risk. In a prospective cohort study of 288 patients with MAFLD, of whom 26 (9.1%) experienced an incident CV event, advanced fibrosis (stage 3–4) on biopsy was shown to be a significant predictor of incident CVD (HR=2.86; 95% CI: 1.36–6.04).[9]

There exists a bidirectional relationship between MAFLD and T2DM

The relationship between MAFLD and T2DM is complex.[10] Though the mechanisms underlying the relationship are complex and not completely understood, it is known that MAFLD promotes worsening insulin resistance and increases the risk of T2DM, atherogenic dyslipidaemia and CVD, while T2DM increases the risk of NASH, cirrhosis and HCC.[10]

CV risk should be assessed in patients with MAFLD

SCORE2, a prediction model to estimate 10-year fatal and non-fatal CVD risk in individuals without previous CVD or diabetes (aged 40–69 years) in Europe, incorporates typical CV risk factors, such as age, smoking, blood pressure and cholesterol levels.[11] However, there is a need to develop a tool that evaluates the impact of MAFLD and NASH on the prediction of CV events.

Therapeutic approaches for managing MAFLD and associated comorbidities

Therapeutic approaches include strategies for weight loss, treatment of T2DM and other cardiometabolic comorbidities, liver-directed treatment and reducing end-stage complications. In addition, EPL has been shown to exert many potential benefits in liver diseases, including regeneration of liver cells,[12–14] detoxification,[15–17] and cell-protective effects.[12,14,17] In the RESTORE study, which ranked the five most recommended supportive treatments by the top three criteria among GEs and GPs, the top three criteria were efficacy, tolerability and quality of life improvement, and EPL was regarded as having a good efficacy and tolerability in comparison with other interventions.[18] Moreover, a direct meta-analysis of RCTs comparing the effect of treatment with EPL + AD versus AD therapy alone, indicates that EPL + AD was associated with a significantly greater reduction in ALT (p=0.0003), triglyceride (p<0.0001) and total cholesterol (p<0.0001) levels than AD alone.[19]

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AD, antidiabetic; ALT, alanine aminotransferase; CAD, coronary artery disease; CI, confidence interval; CIMT, carotid intima-media thickness; CV, cardiovascular; CVD, cardiovascular disease; EPL, essential phospholipids; GE, gastroenterologist; GP, general practitioner; HCC, hepatocellular carcinoma; HR, hazard ratio; MAFLD, metabolic-dysfunction associated fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomised controlled trial; T2DM, type 2 diabetes mellitus.

Learning objectives:

- Describe the paradigm shift from NAFLD to MAFLD and its implications for clinical practice
- Discuss the bidirectional association between cardiometabolic disorders (such as CVD and T2DM) and NAFLD
- Provide an overview of the hepatic effects of using statins and AD drugs for patients with NAFLD and cardiometabolic disorders

Main takeaways:

- Patients with NAFLD are considered at higher risk for both the presence of T2D and CVD due to insulin resistance and atherogenic lipoprotein phenotype
- In patients with MAFLD, the risk of CV events should be assessed
- Statins, management of hypertension, and pioglitazone or GLP-1RA in prediabetes/T2DM are of proven efficacy in decreasing both the steatosis and inflammation in the liver and CVD risk
- EPL have demonstrated many benefits in liver diseases, including steatosis and improvement in blood lipid levels, with a good efficacy and tolerability when compared with other similar interventions

AD, antidiabetic; CVD, cardiovascular disease; EPL, essential phospholipids; GLP-1RA, glucagon-like peptide-1 receptor agonist; MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

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