Metabolic associated fatty liver disease and cardiovascular risk: The expert opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society

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ABSTRACT

The diagnosis of metabolic associated fatty liver disease (MAFLD) is significant for patients' prognosis, as the disease accelerates the development of cardiovascular complications and, on the other hand, cardiometabolic conditions are risk factors for the development of fatty liver diseases. This expert opinion presents principles of MAFLD diagnosis and standards of management to reduce cardiovascular risks in patients with MAFLD.

Key words: atherosclerotic cardiovascular disease, cardiovascular risk, metabolic associated fatty liver disease, obesity, statin

INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) is a common medical condition while visceral obesity is its most frequent underlying reason. MAFLD promotes the occurrence of other components of metabolic syndrome [1–3]. Patients with MAFLD are more prone to cardiovascular conditions, including atherosclerotic cardiovascular disease (ASCVD) than persons with normal liver function [4, 5].

The fairly high prevalence of non-alcoholic steatohepatitis (NASH) is a significant observation, as this condition precedes the development of serious hepatological consequences in patients with MAFLD. The incidence of NASH is rather difficult to estimate. Since NASH has to be confirmed by a histopathological evaluation, its exact diagnosis, in terms of proper methodology, can be obtained only in some patients. Following current estimates, NASH affects 2.5%–5% of the adult population. Progressive fibrosis will develop in about 40% of patients with NASH [6]. Regarding patients with MAFLD, but without NASH, disease progression is also observed but at a much slower rate [7]. NASH and its consequences are estimated to occur much more frequently than any other liver disease.

This expert opinion aims to outline principles of MAFLD diagnosis, methods of identification of the groups of patients in whom MAFLD should be diagnosed, and management procedures to reduce cardiovascular risks in patients with MAFLD.

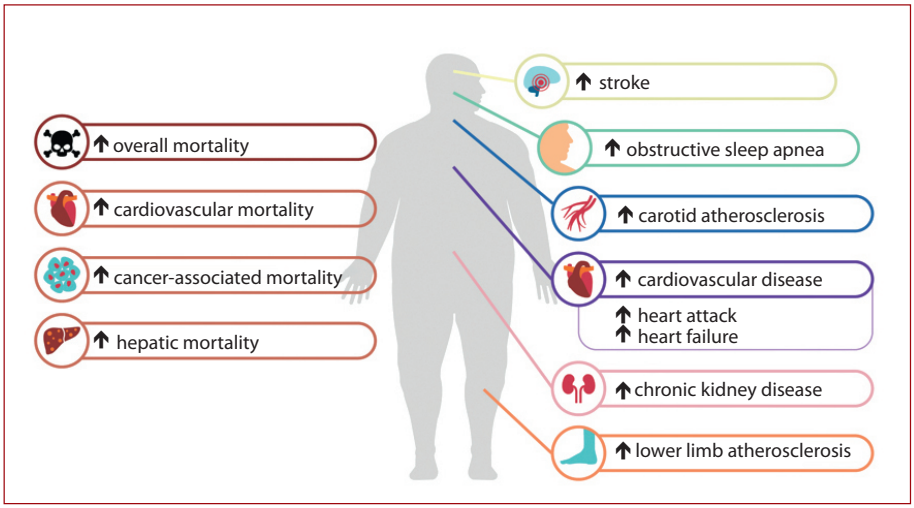

Figure 1. Hepatic and extrahepatic conditions, observed in patients with fatty liver disease, based on [12, 17], modified

THE DIAGNOSIS OF MAFLD

The overall prevalence of MAFLD is estimated at 25% of the general population in developed countries. According to the definition proposed in 2020, MAFLD affects the following subjects: overweight/obese individuals with type 2 diabetes mellitus (T2DM) and normal weight persons fulfilling at least 2 criteria, mainly metabolic ones. The diagnosis of hepatic steatosis in normal weight individuals, referred to by the English term "lean NAFLD", may be an issue in clinical practice. The risk factors for its occurrence are still insufficiently recognized or understood. Some patients present metabolic disorders and specific genetic mutations in mitochondrial enzymes [8, 9]. The current division of fatty liver disease into alcoholic and non-alcoholic has been raising many controversies. Indeed, alcohol consumption may induce steatosis of the liver. However, it is increasingly suggested that, especially in these cases, metabolic effects are likely to outweigh toxic effects of alcohol.

The clinical diagnosis is obtained via assessment of risk factors for MAFLD [8, 9]. The diagnostic criteria for MAFLD include:

- Obesity or overweight, defined as a body mass index (BMI) ≥25 kg/m^2;
- T2DM;
- The occurrence of at least 2 of the following factors, irrespective of BMI:
  - abdominal obesity waist circumference ≥102/88 cm in men/women;
  - pre-diabetes, defined as fasting glucose level: 100–125 mg/dl (5.6–6.9 mmol/l) or in 2 hours after glucose load: 140–199 mg/dl (7.8–11 mmol/l) or glycated hemoglobin level: 5.7%–6.4% (39––47 mmol/mol);
  - arterial blood pressure ≥130/85 mm Hg or antihypertensive treatment;
  - serum triglyceride level ≥150 mg/dl (1.7 mmol/l) or lipid-lowering treatment;
  - high-density lipoprotein cholesterol (HDL-C) level <40 mg/dl (1.0 mmol/l) for men and <50 mg/dl (1.3 mmol/l) for women;
  - Homeostatic Model Assessment — Insulin Resistance (HOMA-IR) ≥2.5;
  - high-sensitivity C-reactive protein (hs-CRP) level >2 mg/l.

The diagnosis of MAFLD requires demonstration of hepatic steatosis by diagnostic imaging (non-invasive methods) and/or histopathology (liver biopsy) and ruling out any other cause of steatosis/liver disease. The other most common reasons for hepatic steatosis include alcohol abuse, hepatitis C virus infection, drugs, parenteral nutrition, Wilson's disease, and malnutrition. In addition, differential diagnosis should take into account hemochromatosis, autoimmune liver disease, or alpha-1-antitrypsin deficiency [8]. MAFLD may be concomitant with other diseases. Detailed differential diagnostics is particularly important when advanced liver fibrosis and/or NASH is present.

MAFLD AND CARDIOVASCULAR PROGNOSIS

The 2021 guidelines of the European Society of Cardiology (ESC) for the prevention of cardiovascular conditions identify MAFLD as a condition to be considered in cardiovascular risk assessment. It was emphasized that MAFLD was associated with increased risk of myocardial infarction and stroke [10]. Also, a document on MAFLD and cardiovascular risk, issued by the American Society of Cardiology, emphasized that MAFLD was a common condition with a multidirectional relationship with cardiovascular diseases [11]. The consequences of MAFLD include, of course, hepatitis, hepatic fibrosis, and finally cirrhotic remodeling of the liver with increased risk of primary liver cancer. Regarding patients with advanced cirrhosis, liver failure and cancer are the most common reasons for death. Notably, the majority of patients with MAFLD may present a benign clinical course of liver disease/condition, whereas cardiovascular diseases become the main reason for premature death [12] (Figure 1).

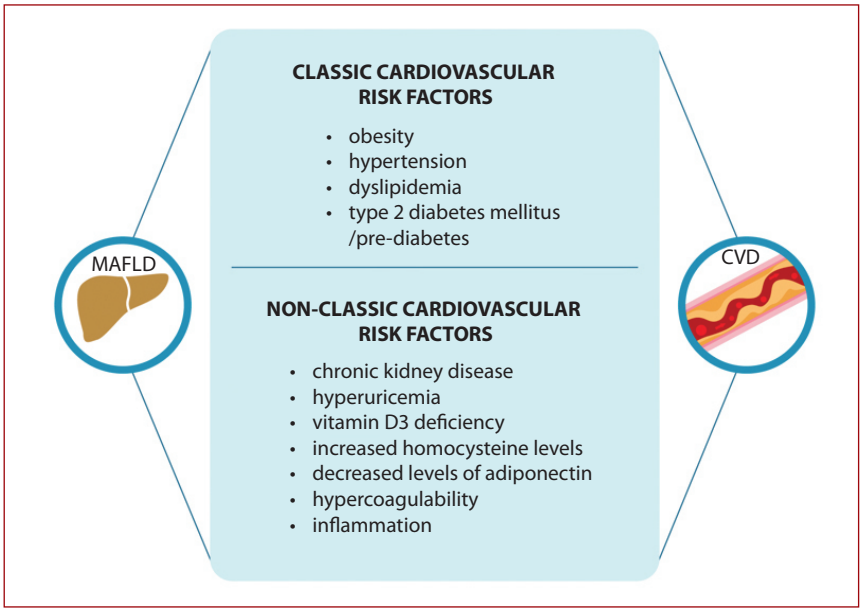

Figure 2. Multidirectional effects of fatty liver disease on the development of cardiovascular complications based on [19], modified

Abbreviations: CVD, cardiovascular disease; MAFLD, metabolic associated fatty liver disease

In the group of patients with MAFLD, cardiovascular deaths were recorded in 43% of patients during a 33-year follow-up [13]. An observational study (the mean follow-up period of 19 years) of patients with a liver biopsy-confirmed diagnosis of MAFLD showed that cardiovascular events had occurred in 28% of the subjects with MAFLD and 21% of the subjects with normal liver function [14]. In turn, a population-based evaluation from the Framingham study reported that hepatic steatosis had been associated with coronary artery and abdominal aortic calcifications, regardless of the presence of other conditions that had been enhancing the cardiovascular risk [15]. Lee et al. [16] obtained computed tomography scans of the coronary artery in asymptomatic patients without a history of cardiovascular events and showed that MAFLD had predisposed to non-calcified atherosclerotic plaques while the degree of fibrosis and hepatic steatosis had correlated with their prevalence. In a meta-analysis, involving 12 620 736 patients, MAFLD had increased the risk of total, all-cause, and cardiovascular mortality compared to patients without MAFLD. Patients with MAFLD demonstrated an increased risk of cardiovascular events, stroke, and chronic kidney disease [17]. In another meta-analysis, including 10 576 383 patients with MAFLD and normal weight, after excluding obesity as a significant factor for a cardiovascular prognosis, cardiovascular events had been common in patients with MAFLD (18.7/1000 person-years) [18].

The high prevalence of cardiovascular conditions in patients with MAFLD is a result of the complex correlation between hepatic steatosis and classical and non-classical cardiovascular risk factors, commonly observed in this particular population (Figure 2) [19]. The majority of patients with MAFLD demonstrate insulin resistance, hypertension, dyslipidemia, overweight, or obesity [20, 21]. In addition, MAFLD is associated with a high prevalence of non-classic cardiovascular risk factors, i.e. chronic kidney disease, hyperuricemia, low vitamin D levels, and low adiponectin levels [22–24].

The mechanisms of ASCVD development in patients with MAFLD are multidirectional. MAFLD induces insulin resistance, increases hepatic glucose synthesis, and significantly affects the lipid profile. These mechanisms coexist with enhanced oxidative stress, impaired fibrinolysis, and increased blood clotting. In addition, in patients with MAFLD, excess of visceral adipose tissue and its hormonal dysfunction is observed, with increased leptin and decreased adiponectin levels. Given the imbalance between anti-inflammatory factors and increased production of pro-inflammatory cytokines and of increased pro-coagulant activity and dyslipidemia in patients with MAFLD, atherosclerotic mechanisms begin to be activated [25–27].

It has been shown that cardiovascular conditions, other than ASCVD, are more common in patients with MAFLD than in the population without liver disease. A meta-analysis of nine studies involving 364 919 patients showed that MAFLD was a predisposing factor to atrial fibrillation [28]. Ventricular arrhythmias were also shown to be more frequent in patients with MAFLD [29]. A meta-analysis of 12 studies, involving 280 000 patients, demonstrated that heart failure with preserved left ventricular systolic function in patients with well-controlled T2DM and MAFLD occurred independently of other risk factors [30].

PRACTICAL DIAGNOSTIC TIPS

Taking into account the frequent concomitance of MAFLD, cardiovascular and metabolic conditions, MAFLD should actively be screened in patients with cardiovascular and metabolic diseases. We propose to carry out diagnostic examinations for MAFLD in patients with:

- T2DM/pre-diabetes;
- dyslipidemia;
- hypertension;

- overweight/obesity;
- ASCVD;
- increased activity of hepatic enzymes.

On the other hand, given that cardiovascular complications including ASCVD are more likely to develop in patients with MAFLD than in patients with a healthy liver, we recommend performing the following examinations in patients with MAFLD:

- BMI and waist circumference measurements;
- blood pressure measurements at home and in a surgery;
- glucose and uric acid level and lipid profile tests;
- electrocardiographic examination;
- ultrasonography imaging of the carotid arteries.

MAFLD AND LIPID DISORDERS

Patients with MAFLD demonstrate proatherogenic lipid profiles, characterized by high triglyceride levels, low-density lipoprotein cholesterol (LDL-C), reduced HDL-C, and high apolipoprotein B (apoB) levels. MAFLD sometimes coexists with hypobetalipoproteinemia, which is a rare pathology characterized by low LDL-C <50 mg/dl resulting from mutations in the apoB encoding gene. In the course of hypobetalipoproteinemia, there is an increased synthesis of cholesterol of the very low-density lipoprotein cholesterol (VLDL) fraction, apoB, and triglycerides. There are no conclusive data on the prognosis of patients with MAFLD and hypobetalipoproteinemia [31].

Cardiovascular risk assessment should be performed in patients with MAFLD and dyslipidemia, according to general principles. As in the majority of patients with MAFLD, this liver disease coexists with metabolic syndrome, and these patients are characterized by high triglyceride and low LDL-C levels, it is worth paying attention to non-HDL-C levels in this group. It reflects the concentration of total cholesterol, transferred by atherogenic apoB-containing lipoproteins, including triglyceride-rich particles and their remnants present in VLDL. According to the 2019 ESC guidelines on dyslipidemia in patients with metabolic disorders, the apoB assay may be an alternative to LDL-C and preferred to non-HDL-C level assays [32].

Following qualification into a specific risk group, lipids targets should be set for patients with dyslipidemia and MAFLD. The main therapeutic target is LDL-C level, while non-HDL-C and apoB levels are additional therapeutic targets [32, 33].

Due to the common prevalence of cardiovascular conditions in patients with MAFLD, they usually present with high cardiovascular risk and require lipid-lowering agents. In patients with MAFLD, statin therapy is very effective in reducing the risk of cardiovascular morbidity and mortality, compared to patients not using statins (68% vs. 39%; $P = 0.007$) [34]. Statins are safe and well-tolerated agents. In rare cases, they can induce side effects, myalgia, and elevated liver enzymes [35]. A transient, asymptomatic increase in liver enzymes occurs in 0.1%–3% of patients while liver failure, due to statin effects, is an extremely rare condition (2 per 100 000 patients) [36]. However, in the vast majority of cases, the elevations of liver enzymes, observed in statin users, do not correlate with the presence of morphological changes in histological evaluations and cannot be thus regarded as indicators of actual liver damage. Despite that, there is a fairly high proportion of patients (1.85%–12%) in whom statin therapy is discontinued due to an increase in liver enzymes [37, 38]. The discontinuation of lipid-lowering therapy in patients with MAFLD, who present an increase in liver enzymes, which is part of the clinical picture of fatty liver diseases, is undoubtedly an important factor accelerating the development of cardiovascular complications in this particular group of patients. Discontinuation of statin therapy in patients with MAFLD results from concerns that these drugs may exacerbate hepatic steatosis. However, this hypothesis has not been confirmed by the results of clinical trials. On the contrary, chronic statin use in patients with MAFLD has been shown to regress steatotic lesions, reduce inflammatory activity, and even reduce the degree of fibrosis [39]. In a post hoc analysis of the GREACE study, including patients with MAFLD and with moderately elevated liver enzymes, a reduction in cardiovascular mortality was observed in the statin-treated patients while no significant statin-related increase in liver enzymes was observed in these patients [40]. A meta-analysis of 22 studies, involving patients with MAFLD, showed that aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGTP) activities decreased, on average, by one-third of the baseline values during statin therapy [41].

Data also support the safety of ezetimibe use in patients with MAFLD. In the MOZART study, ezetimibe in a dose of 10 mg had no effect on the course of hepatic steatosis [42]. Furthermore, the ESSENTIAL study showed that ezetimibe, in a dose of 10 mg, combined with rosuvastatin in a dose of 5 mg, was safe and reduced fibrosis in patients with MAFLD, compared to those treated with rosuvastatin alone [43].

The selection of a lipid-lowering drug and its dose in patients with dyslipidemia and MAFLD should be guided by its efficacy in achieving the LDL-C target values, as defined for a given cardiovascular risk group [32, 33]. According to an expert opinion, rosuvastatin is the preferred statin in patients with liver disease due to its pharmacokinetic profile [44]. The treatment of both dyslipidemia and MAFLD should start with non-pharmacological management, which will be discussed later. Lipid-lowering therapy should be launched in patients with MAFLD, starting with a potent statin at the highest recommended/tolerated dose and, if the main therapeutic goal is not achieved, ezetimibe should be added, and if this scheme is still ineffective, a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) should be added [32, 33]. According to the currently valid guidelines, liver function monitoring (ALT activity determination)

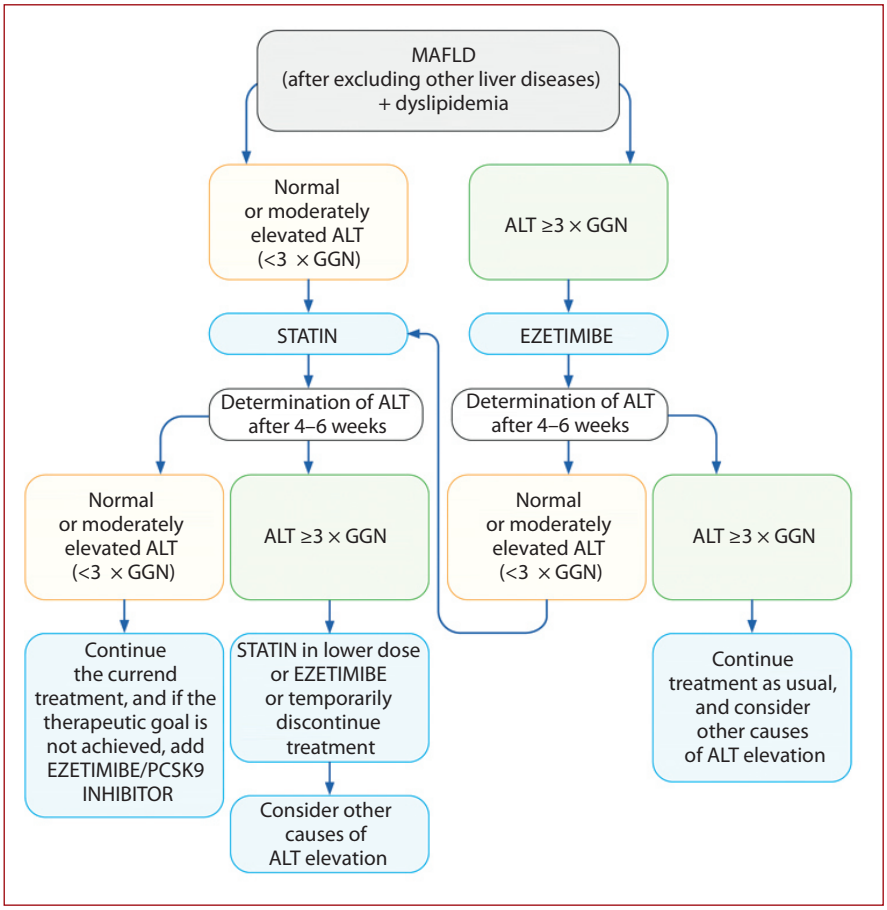

Figure 3. Lipid-lowering therapy initiation algorithm in patients with dyslipidemia and MAFLD

Abbreviations: ALT, alanine aminotransferase; GGN, the upper limit of normal; PCSK9, proprotein convertase subtilisin/kexin type 9; other — see Figure 2

should be performed before the onset of lipid-lowering treatment; it should be then repeated after 4–6 weeks from the therapy starting point [32, 33]. Figure 3 presents a lipid-lowering treatment initiation scheme in patients with dyslipidemia and MAFLD.

MAFLD AND OBESITY

MAFLD usually accompanies abdominal obesity. Hepatic steatosis rarely occurs in patients with normal body weight and normal glucose tolerance. Insulin resistance and impaired fat tissue distribution with an increased waist circumference are usually observed in such cases. Steatosis of the liver occurs in 70%–80% of obese people [45]. A 1% increase in visceral fat deposition increases hepatic lipid accumulation by 40%, and a 1% increase in subcutaneous fat deposition increases hepatic lipid accumulation by 20% [46]. Abdominal ultrasound is recommended in patients with excessive body weight to assess hepatic steatosis [47].

Patients with MAFLD and a BMI ≥25 kg/m^2 are recommended to reduce their body weight by reducing the energy component in the diet and increasing physical activity. BMI reduction by at least 5% is recommended, which significantly decreases hepatic steatosis. A gradual weight reduction is advisable; body weight reduction must not exceed 0.5 kg per week. The objective of diet modification should be the reduction of its energy content by 30% vs. total energy demand, which can be achieved by cutting calories, namely by 750–1000 kcal per day [48]. Diets that are too low in energy, causing rapid weight loss, may contribute to progression of liver lesions. It is recommended to limit simple sugars and saturated fats in the diet in favor of mono- and polyunsaturated fats. Restricting carbohydrate intake, including fructose, is important in the management of obesity in patients with MAFLD. The recommended physical efforts should be of moderate intensity and adapted to the patient's physical capabilities. The weight reduction process in patients with BMI ≥35 kg/m^2, besides dietary recommendations, may require pharmacotherapy and/or bariatric surgery [49].

MAFLD AND T2DM

The development of T2DM in patients with MAFLD is promoted by the following two primary mechanisms: reduced tissue sensitivity to insulin and impaired insulin secretion/generation by pancreatic beta cells. A meta-analysis, including 20 clinical studies and 117 020 patients with an average 5-year follow-up, showed that patients with MAFLD had a twofold increased risk of T2DM, compared to those without fatty liver disease [50]. MAFLD is diagnosed in 70% of patients with T2DM [51]. MAFLD is strongly associated with insulin resistance; patients with MAFLD tend to demonstrate worse glycemic control than those with T2DM and normal liver function. Therapy strategies, aimed at reducing intrahepatic triglyceride levels and improving

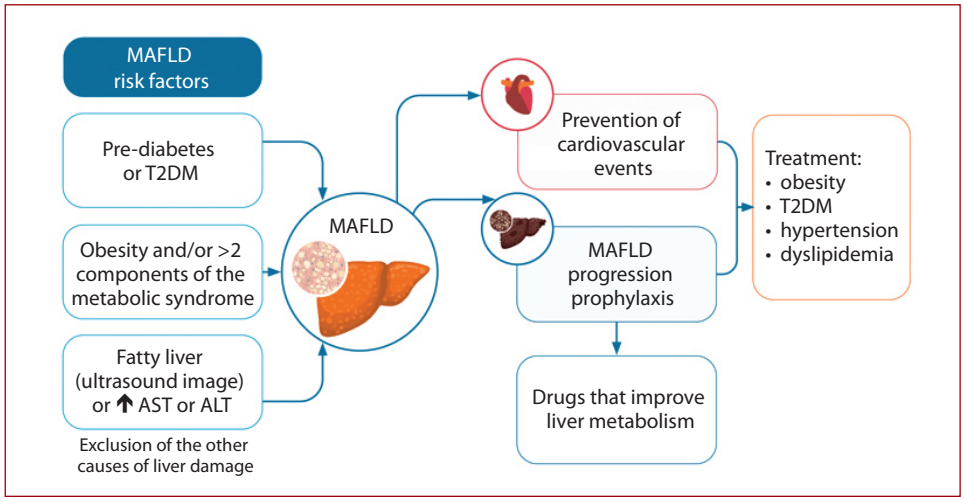

Figure 4. Management improving the prognosis of patients with MAFLD, based on [50], modified

Abbreviations: AST, aspartate aminotransferase; T2DM, type 2 diabetes mellitus; other — see Figures 2 and 3

insulin sensitivity, may result in better glycemic control in patients with T2DM and MAFLD [23]. On the other hand, proper glycemic control is known to limit liver exposure to harmful metabolic factors, so the selection and setup of an optimal treatment regimen for T2DM and MAFLD are the key issues.

The choice of glucose-lowering treatment in patients with T2DM and MAFLD should be based on the efficacy of a given agent to achieve glycemic targets and ensure a potential impact of the drug on body weight reduction. Patients with T2DM and MAFLD are at high risk of cardiovascular events, so the prescribed glucose-lowering drugs should ensure a reduction of their incidence rate. In the Polish 2019 expert opinion on the management of patients with MAFLD, two drugs: pioglitazone and incretin are recommended for patients with concomitant T2DM [49]. Similarly, in the 2022 American Association for the Study of Liver Diseases guidelines, the preferred glucose-lowering drugs in patients with T2DM and MAFLD include pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [47]. The profile of the patient with T2DM and MAFLD should determine the choice of a glucose-lowering drug. In patients with coexisting heart failure and/or chronic kidney disease, SGLT2 inhibitors should be preferred while GLP-1 agonists should be favored in patients with obesity and/or coronary artery disease.

TREATMENT OF MAFLD IN PATIENTS WITH CARDIOVASCULAR CONDITIONS

As MAFLD is rarely isolated and most often occurs with cardiometabolic conditions, and the multidirectional relationship between hepatic steatosis and cardiovascular conditions worsens the prognosis of these patients, a parallel treatment of cardiovascular conditions should be adopted to achieve therapeutic goals. An optimal strategy should include cardiac drugs as well as drugs to improve liver function (Figure 4) [50].

The pharmacological treatment to improve liver function and correct the metabolic abnormalities caused by MAFLD should include drugs with antioxidant, anti-apoptotic, fibrosis-reducing, and hepatocyte metabolism normalizing effects. The drugs that potentially meet these criteria and are available in Poland include vitamin E and ursodeoxycholic acid (UDCA).

Vitamin E, used in high doses of 400–800 IU/day, reduces hepatic steatosis and inflammation but has no significant effect on the fibrosis process [51]. An increased risk of hemorrhagic stroke and the development of prostate cancer in men over 50 years of age are the limitations of this therapy. There are no data on the optimal duration of therapy and no data on the efficacy of vitamin E in patients with T2DM.

UDCA therapy reduces secretion of cholesterol into the bile, probably by reducing its absorption and increasing its conversion to bile acids. UDCA therapy has been shown to improve hepatocyte secretory function and inhibit pro-inflammatory cytokine activity at the cellular level. In a meta-analysis of 12 studies (1160 subjects), in which UDCA was used as monotherapy or in combination with other drugs at doses of 10–35 mg/kg, UDCA decreased ALT activity and reduced hepatic steatosis [52]. Ratziu et al. [53] showed that ALT activity was decreased by 41% and AST activity by 19% by the use of UDCA in patients with MAFLD. Significant improvements in hepatic parameters were noted after merely three months of taking the drug. What is more, in the patients with MAFLD and T2DM using UDCA, there was an additional improvement in carbohydrate management parameters (reduced glucose, insulin, glycated hemoglobin levels, and reduced HOMA-IR index) [53]. UDCA therapy is characterized by good tolerance and a high safety profile. No reports are known of any significant adverse effects during chronic UDCA use in MAFLD. UDCA may thus safely be used in long-term therapies. It is recommended to monitor the efficacy of the treatment after 3–6 months of its duration, and UDCA therapy should be maintained until a reduction in liver enzymes by at least one-third of their baseline value is achieved. No data are

available on whether the listed drugs, used in the treatment of MAFLD, modify cardiovascular risks or affect the rate of cardiovascular complications.

SUMMARY

MAFLD is a medical condition that significantly worsens prognosis and should therefore be actively sought in patients with predisposing factors. As the relationship between MAFLD and cardiovascular diseases is bidirectional, it is recommended to assess the ASCVD risk in patients with MAFLD. Non-pharmacological interventions, aimed at normalizing/maintaining body weight and correcting eating habits, are very important in MAFLD therapy. However, the most important factors for the prognosis of these patients include proper diagnosis and effective treatment of cardiovascular and metabolic conditions.

Article information

Conflict of interest: IGG — Bayer, Boehringer Ingelheim, KRKA, Novo Nordisk, Promed. MW — AstraZeneca, Egis, Novartis, Novo Nordisk, Polpharma, Pomed, Adamed, Apotex, Aurovitas, Bayer, Berlin Chemie, Boehringer Ingelheim, KRKA, Pfizer, Sandoz, Sanofi-Avensis, Servier, Teva. AM — Adamed, AstraZeneca, Aurovitas Pharma, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Celon, Egis, Gedeon Richter, KRKA, Lilly, MSD, Novo Nordisk, Pfizer, Polpharma, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. KJF — Adamed, AstraZeneca, Bausch Health, Bayer, Boehringer Ingelheim, Egis, KRKA, Mundipharma, Novartis, Pfizer, Sandoz, Servier, Viatris. BWK — Adamed, Bausch Health, Bayer, Biofarm, Boehringer Ingelheim, Egis, Gedeon Richter, KRKA, Pfizer, Sandoz, Servier, USP Zdrowie. MB — Adamed, Aurovitas Pharma, Bausch Health, Bayer, Biofarm, Bioton, Boehringer Ingelheim, Egis, Gedeon Richter, Krka, Merck, MSD, Pfizer, Polfarmex, Ranbaxy, Recordati, Sandoz, Sanofi, Servier, USP Zdrowie, Viatris, Zentiva. FS — Adamed Pharma, AstraZeneca, Boehringer Ingelheim, ProMed, KRKA, Viatris. JDK declares no conflict of interest. KT — AbbVie, Gilead, AstraZeneca, MSD, Pfizer, Promed, Roche.

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REFERENCES

1. Pimpin L, Cortez-Pinto H, Negro F, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018; 69(3): 718–735, doi: 10.1016/j.jhep.2018.05.011, indexed in Pubmed: 29777749.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67(1): 328–357, doi: 10.1002/hep.29367, indexed in Pubmed: 28714183.
3. Angelico F, Del Ben M, Conti R, et al. Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. J Gastroenterol Hepatol. 2003; 18(5): 588–594, doi: 10.1046/j.1440-1746.2003.02958.x, indexed in Pubmed: 12702052.
4. Käräjämäki AJ, Bloigu R, Kauma H, et al. Non-alcoholic fatty liver disease with and without metabolic syndrome: Different long-term outcomes. Metabolism. 2017; 66: 55–63, doi: 10.1016/j.metabol.2016.06.009, indexed in Pubmed: 27423871.
5. Stahl EP, Dhindsa DS, Lee SK, et al. Nonalcoholic fatty liver disease and the Heart: JACC state-of-the-art review. J Am Coll Cardiol. 2019; 73(8): 948–963, doi: 10.1016/j.jacc.2018.11.050, indexed in Pubmed: 30819364.
6. Wong VWS, Wong GLH, Choi PCL, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut. 2010; 59(7): 969–974, doi: 10.1136/gut.2009.205088, indexed in Pubmed: 20581244.
7. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015; 13(4): 643–654.e9, doi: 10.1016/j.cgh.2014.04.014, indexed in Pubmed: 24768810.
8. Eslam M, Sanyal AJ, George J, et al. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020; 158(7): 1999–2014.e1, doi: 10.1053/j.gastro.2019.11.312, indexed in Pubmed: 32044314.
9. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020; 73(1): 202–209, doi: 10.1016/j.jhep.2020.03.039, indexed in Pubmed: 32278004.
10. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2022; 29(1): 5–115, doi: 10.1093/eurjpc/zwab154, indexed in Pubmed: 34558602.
11. Duell PB, Welty FK, Miller M, et al. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2022; 42(6): e168–e185, doi: 10.1161/ATV.0000000000000153, indexed in Pubmed: 35418240.
12. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015; 313(22): 2263–2273, doi: 10.1001/jama.2015.5370, indexed in Pubmed: 26057287.
13. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015; 61(5): 1547–1554, doi: 10.1002/hep.27368, indexed in Pubmed: 25125077.
14. Hagström H, Nasr P, Ekstedt M, et al. Cardiovascular risk factors in non-alcoholic fatty liver disease. Liver Int. 2019; 39(1): 197–204, doi: 10.1111/liv.13973, indexed in Pubmed: 30253056.
15. Mellinger JL, Pencina KM, Massaro JM, et al. Hepatic steatosis and cardiovascular disease outcomes: An analysis of the Framingham Heart Study. J Hepatol. 2015; 63(2): 470–476, doi: 10.1016/j.jhep.2015.02.045, indexed in Pubmed: 25776891.
16. Lee SB, Park GM, Lee JY, et al. Association between non-alcoholic fatty liver disease and subclinical coronary atherosclerosis: An observational cohort study. J Hepatol. 2018; 68(5): 1018–1024, doi: 10.1016/j.jhep.2017.12.012, indexed in Pubmed: 29274406.
17. Quek J, Ng CH, Tang AS, et al. Metabolic associated fatty liver disease increases the risk of systemic complications and mortality. A meta-analysis and systematic review of 12 620 736 individuals. Endocr Pract. 2022; 28(7): 667–672, doi: 10.1016/j.eprac.2022.03.016, indexed in Pubmed: 35364328.
18. Ye Q, Zou B, Yeo YH, 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, indexed in Pubmed: 32413340.
19. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013; 10(6): 330–344, doi: 10.1038/nrgastro.2013.41, indexed in Pubmed: 23507799.
20. Targher G, Corey KE, Byrne CD, et al. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. Nat Rev Gastroenterol Hepatol. 2021; 18(9): 599–612, doi: 10.1038/s41575-021-00448-y, indexed in Pubmed: 33972770.
21. Kalavalapalli S, Leiva EG, Lomonaco R, et al. Metabolic impact of non-alcoholic steatohepatitis in obese patients with type 2 diabetes. Diabetes Care. 2016; 39(4): 632–638, doi: 10.2337/dc15-1876, indexed in Pubmed: 26861926.
22. Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. J Hepatol. 2020; 72(4): 785–801, doi: 10.1016/j.jhep.2020.01.013, indexed in Pubmed: 32059982.

23. Targher G, Bertolini L, Scala L, et al. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis. 2007; 17(7): 517–524, doi: 10.1016/j.numecd.2006.04.002, indexed in Pubmed: 16928437.
24. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. Clin Endocrinol (Oxf). 2006; 64(6): 679–683, doi: 10.1111/j.1365-2265.2006.02527.x, indexed in Pubmed: 16712671.
25. Kim D, Kim WR, Kim HJ, et al. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013; 57(4): 1357–1365, doi: 10.1002/hep.26156, indexed in Pubmed: 23175136.
26. Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology. 2005; 42(3): 641–649, doi: 10.1002/hep.20842, indexed in Pubmed: 16116629.
27. Sookoian S, Castaño GO, Burgueño AL, et al. Circulating levels and hepatic expression of molecular mediators of atherosclerosis in nonalcoholic fatty liver disease. Atherosclerosis. 2010; 209(2): 585–591, doi: 10.1016/j.atherosclerosis.2009.10.011, indexed in Pubmed: 19896127.
28. Mantovani A, Dauriz M, Sandri D, 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, indexed in Pubmed: 30657626.
29. Mantovani A, Rigamonti A, Bonapace S, et al. Nonalcoholic fatty liver disease is associated with ventricular arrhythmias in patients with type 2 diabetes referred for clinically indicated 24-hour holter monitoring. Diabetes Care. 2016; 39(8): 1416–1423, doi: 10.2337/dc16-0091, indexed in Pubmed: 27222503.
30. Wijarnpreecha K, Lou S, Panjawatanan P, et al. Association between diastolic cardiac dysfunction and nonalcoholic fatty liver disease: A systematic review and meta-analysis. Dig Liver Dis. 2018; 50(11): 1166–1175, doi: 10.1016/j.dld.2018.09.004, indexed in Pubmed: 30292566.
31. Corey KE, Misdraji J, Gelrud L, et al. Nonalcoholic steatohepatitis is associated with an atherogenic lipoprotein subfraction profile. Lipids Health Dis. 2014; 13: 100, doi: 10.1186/1476-511X-13-100, indexed in Pubmed: 24952382.
32. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1): 111–188, doi: 10.1093/eurheartj/ehz455, indexed in Pubmed: 31504418.
33. Szymański FM, Mickiewicz A, Dzida G, et al. Management of dyslipidemia in Poland: Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. The Fourth Declaration of Sopot. Cardiol J. 2022; 29(1): 1–26, doi: 10.5603/CJ.a2021.0147, indexed in Pubmed: 34811718.
34. Lai SW, Liao KF, Lai HC, et al. Statin use and risk of hepatocellular carcinoma. Eur J Epidemiol. 2013; 28(6): 485–492, doi: 10.1007/s10654-013-9806-y, indexed in Pubmed: 23681775.
35. Adhyaru BB, Jacobson TA. Safety and efficacy of statin therapy. Nat Rev Cardiol. 2018; 15(12): 757–769, doi: 10.1038/s41569-018-0098-5, indexed in Pubmed: 30375494.
36. Bhardwaj SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. Clin Liver Dis. 2007; 11(3): 597–613, vii, doi: 10.1016/j.cld.2007.06.010, indexed in Pubmed: 17723922.
37. Newman C, Tsai J, Szarek M, et al. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. Am J Cardiol. 2006; 97(1): 61–67, doi: 10.1016/j.amjcard.2005.07.108, indexed in Pubmed: 16377285.
38. Wei MY, Ito MK, Cohen JD, et al. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. J Clin Lipidol. 2013; 7(5): 472–483, doi: 10.1016/j.jacl.2013.03.001, indexed in Pubmed: 24079289.
39. Ekstedt M, Franzén LE, Mathiesen UL, et al. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. J Hepatol. 2007; 47(1): 135–141, doi: 10.1016/j.jhep.2007.02.013, indexed in Pubmed: 17400325.
40. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010; 376(9756): 1916–1922, doi: 10.1016/S0140-6736(10)61272-X, indexed in Pubmed: 21109302.
41. Lai SW, Liao KF, Lai HC, et al. Statin use and risk of hepatocellular carcinoma. Eur J Epidemiol. 2013; 28(6): 485–492, doi: 10.1007/s10654-013-9806-y, indexed in Pubmed: 23681775.
42. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology. 2015; 61(4): 1239–1250, doi: 10.1002/hep.27647, indexed in Pubmed: 25482832.
43. Cho Y, Rhee H, Kim YE, et al. Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: an open-label randomized controlled trial (ESSENTIAL study). BMC Med. 2022; 20(1): 93, doi: 10.1186/s12916-022-02288-2, indexed in Pubmed: 35307033.
44. Filipiak KJ. Atorvastatin and rosuvastatin – what's new for patients in the 2016 European Society of Cardiology guidelines regarding dyslipidemia? Statins – which ones and in what doses? [in Polish]Kardiol Pol. 2017; 75(I): 1–12, doi: 10.5603/kp.2017.0012.
45. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology. 2008; 48(2): 449–457, doi: 10.1002/hep.22350, indexed in Pubmed: 18627003.
46. Thomas EL, Hamilton G, Patel N, et al. Hepatic triglyceride content and its relation to body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy study. Gut. 2005; 54(1): 122–127, doi: 10.1136/gut.2003.036566, indexed in Pubmed: 15591516.
47. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022; 28(5): 528–562, doi: 10.1016/j.eprac.2022.03.010, indexed in Pubmed: 35569886.
48. Reddy JK. Nonalcoholic steatosis and steatohepatitis. III. Peroxisomal beta-oxidation, PPAR alpha, and steatohepatitis. Am J Physiol Gastrointest Liver Physiol. 2001; 281(6): G1333–G1339, doi: 10.1152/ajpgi.2001.281.6.G1333, indexed in Pubmed: 11705737.
49. Hartleb M, Wunsch E, Milkiewicz P, et al. Management of patients with non-alcoholic fatty liver disease. The 2019 guidelines of the Polish Group of Experts on NAFLD [in Polish]. Med Prakt. 2019; 10: 13–14.
50. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016; 31(5): 936–944, doi: 10.1111/jgh.13264, indexed in Pubmed: 26667191.
51. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018; 67(1): 328–357, doi: 10.1002/hep.29367, indexed in Pubmed: 28714183.
52. Xiang Z, Chen Yp, Ma Kf, et al. The role of ursodeoxycholic acid in non-alcoholic steatohepatitis: a systematic review. BMC Gastroenterol. 2013; 13: 140, doi: 10.1186/1471-230X-13-140, indexed in Pubmed: 24053454.
53. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol. 2011; 54(5): 1011–1019, doi: 10.1016/j.jhep.2010.08.030, indexed in Pubmed: 21145828.