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## **A new name for an old problem. Metabolic dysfunction-associated steatotic liver disease - review of literature**

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## Abstract

**Introduction:** Metabolic dysfunction-associated steatotic liver disease (MASLD) was previously known as non-alcoholic fatty liver disease (NAFLD). MASLD is one of the most important and leading causes of liver disease worldwide. This disease is a public health challenge in the 21st century.

**Aim of the study:** This article aims to present the latest literature data on MASLD. The study is intended to show what consequences are associated with changing the name of the disease and this article is purposive to be a vademecum of knowledge for practicing physicians.

**Material and methods:** Comprehensive literature searches were performed across the main electronic databases of PubMed and GoogleScholar using the keywords: "metabolic-dysfunction associated steatotic liver disease", "MASLD", "non-alcoholic fatty liver disease" and "NAFLD"

**Conclusions:** Most patients do not report any symptoms. It is important to identify patients at increased risk of MASLD. A fundamental role in prevention and treatment is lifestyle changes. The pharmacological approach includes among others use of antidiabetic drugs and treatment of other associated states.

**Keywords:** "metabolic-dysfunction associated steatotic liver disease", "MASLD", "non-alcoholic fatty liver disease", "NAFLD"

## **Introduction**

It is estimated, that MASLD, which formerly was known as NAFLD, affects up to one-third of the global population [1, 2]. The disease is often asymptomatic, and when symptoms appear, they are non-specific [3]. It is critical to understand that NAFLD can progress and be associated with serious complications such as increased risk of hepatocellular carcinoma (HCC) and other cancers or end-stage liver disease, and even death [2].

## **Epidemiology**

The literature reported that in recent years the worldwide prevalence of metabolic-related disorders has increased. The global prevalence of MASLD increased by 50.4% from 25.3% in 1990–2006 to 38.2% in 2016–2019 [1]. However, there is variation in the frequency of disease occurrence depending on the geographical region. MASLD was found to be most prevalent in the Middle East (31.8%), followed by South America (30.4%). On the other hand, MASLD is less common in Africa (13.5%). Comparatively, the prevalence of MASLD in Asia, North America, and Europe was found to be 27.4%, 24.1% and 23.7% respectively [4]. The prevalence of the disease among the pediatric population is lower (7.4%) than among adults (30%). At the global level, the male-to-female ratio for all-age age-standardized MASLD prevalence was 1.21 [5].

## **Risk factors**

Patients with type 2 diabetes mellitus (T2DM) are one of the target groups who should be searched for MASLD. Obesity and insulin resistance are key pathogenic factors for both MASLD and T2DM and thus, these two pathologic conditions commonly coexist [6]. Excess body weight is closely related to metabolic diseases including MASLD [7]. Being overweight in childhood and adolescence is associated with an increased risk of disease later in life [8]. Moreover, obesity could predict a worse long-term prognosis in MASLD patients [9]. Furthermore, MASLD is known to be associated with hypertension and hypertriglyceridemia [10]. Also among risk factors are non-synonymous single nucleotide polymorphisms (SNPs) in two genes in particular, *PNPLA3* (encoding patatin-like phospholipase domain-containing protein 3) and *TM6SF2* (encoding transmembrane 6 superfamily member 2) [8].

One of the most significant and reproducible genetic variants linked with MASLD is a missense mutation in *PNPLA3* which leads to isoleucine to methionine substitution at position 148 (rs738409 C>G encoding for *PNPLA3* I148M) [4, 11]. The occurrence of the polymorphism in

*PNPLA3* varies depending on racial groups and it was estimated to be found in 49% of Hispanics, 23% in white persons, and 17% in black persons [11]. *PNPLA3* exerts a relevant influence on fat accumulation in the liver in GG homozygous persons showing 73% more hepatic fat content when compared with CC homozygous individuals. Additionally, people with this mutation are also more susceptible to the development of more severe histologic hepatic damage, with a 3.24-fold greater risk of higher necro-inflammatory scores and a 3.2-fold greater risk of developing fibrosis [4].

### **Etiopathogenesis**

This condition is characterized by excessive deposition of lipids in hepatocytes, which leads to metabolic liver injury [10]. The main lipids which are accumulating are triglycerides (TG). They are formed as a result of esterification of intrahepatic free fatty acids (FFA) with glycerol. There are 3 sources of FFA from which then TG is created, accounted for 59% comes from circulating FFA; 26%, from the generation of FFA from nonlipid precursors (including glucose and fructose) through de novo lipogenesis (DNL); and 14%, from the diet. Alternatively, FFA can be metabolized by beta-oxidation for the generation of adenosine triphosphate (ATP), specifically in the mitochondria; or TG can be exported from the liver to the systemic circulation as constituents of very-low-density lipoproteins (VLDL) [11]. Excessive beta-oxidation of FFA results in the production of reactive oxygen species and cytotoxic species which lead to oxidative stress [12].

A study by Zhang et al. showed that serum FFA levels were markedly higher in patients with MASLD than in healthy control participants [13]. One of the reasons, why FFA delivery to the liver is increasing is insulin resistance [14]. As insulin inhibits lipolysis in the adipocytes, insulin resistance in the adipose tissue causes increased release of FFA [15]. MASLD is strongly associated with reduced whole-body insulin sensitivity, as well as increased hepatic and adipose tissue insulin resistance [14]. The role of insulin is to reduce hepatic glucose production by inhibiting glycogenolysis during food intake and limiting the postprandial rise in glucose levels in the blood. In insulin resistance, this feedback mechanism is impaired, and hepatic glucose production continues to rise even when postprandial glucose increases [16].

It is also noted, that in patients with MASLD is increased hepatic de novo lipogenesis. In the literature, we can find information, that overconsumption of added dietary sugars, especially fructose, precipitates hepatic steatosis due to complex mechanisms that ultimately promote increased lipogenesis and impaired fatty acid oxidation [17]. In contrast to glucose, fructose is rapidly phosphorylated by fructokinase leading to a reduction in ATP. This decrease in ATP induces a cascade of impaired protein synthesis, oxidative stress and mitochondrial dysfunction

[11]. Reducing the consumption of free sugars can significantly improve hepatic steatosis [17]. Based on research where isotopes were used, patients with MASLD had a threefold increase in DNL and higher nocturnal plasma levels of FFA [15]. Moreover, the levels of two key enzymes in DNL, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), are elevated in MASLD patients, implying that DNL plays an essential role in lipid deposition [10].

The intrahepatic beta-oxidation of FFA belongs to one of the mitochondrial functions [11]. Increased hepatic fat would increase hepatic fat oxidation with increased mitochondrial respiration, however, in patients with MASLD was found that the efficiency of respiratory chain complexes was decreased. Chronic mitochondrial dysfunction due to the state of lipid overload leads to excessive leakage of electrons from mitochondrial respiratory complexes, causing oxidative stress [14]. Research by Marjot et al. pointed out that mitochondrial-derived reactive oxygen species (ROS) have a central role in propagating hepatocyte injury by generating both lipid peroxidation products and tumor necrosis factor-alpha (TNF- $\alpha$ ), both of which induce further mitochondrial damage, permeability, and uncoupling [11].

Furthermore, factors influencing pathogenesis also include epigenetic factors, lysosomal dysfunction, and endoplasmic reticulum (ER) stress [14]. Therefore, future research may focus on still not completely known factors to identify for example liver-specific ER stress modulators.

### **Clinical presentation**

MASLD is often described as being asymptomatic in most patients [2]. This is the reason, why recognition of MASLD, especially in the early stage of the disease, can be a serious challenge for physicians. The diagnosis may be made incidentally after carrying out a routine laboratory examination or during a work-up of frequent chronic disorders such as hypertension, diabetes, and dyslipidemia. Some patients, especially children, complain of fatigue and malaise, but these symptoms are not specific [18]. Some patients with MASLD report experiencing abdominal pain, especially in the right upper quadrant of the abdomen [2, 19]. It is suggested that the presence of this pain may be caused by distension of the capsule that surrounds the liver, known as the Glisson's capsule. This is a thin tissue that contains pain receptors, which can sense swelling or distension of the liver. While abdominal symptoms are the most commonly reported in individuals with MASLD, a smaller number of patients may report other nonspecific symptoms. Patients may complain about psychological symptoms like anxiety, depression; general pain, and sleep disturbances like sleep apnea, and tiredness [2].

The complete physical examination is obligatory, and it should include measurement of height, weight, waist-to-hip ratio, and blood pressure [3]. There are no characteristic findings that can

be detected during physical examination, but common are central obesity and hepatomegaly [19]. It is worth noticing, that hepatomegaly has been reported in up to 50% of patients with MASLD [18]. The rare finding is a splenomegaly [3]. Also, patients may have an acanthosis nigricans which is a cutaneous marker of insulin resistance, which is more pronounced when disease is more advanced [19].

Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) concentrations could be mild to moderately increased, up to 1–4 times the upper limits of reference values, with an AST/ALT ratio  $< 1$  [18]. However, ALT and AST levels may also be within the normal range and therefore the disease and fibrosis cannot be excluded based on their normal serum concentration [3, 19]. Among laboratory abnormalities also could be elevated serum levels of gamma-glutamyl transpeptidase and ferritin. Usually, liver function tests, such as serum albumin, bilirubin, and prothrombin time, are normal [18]. In addition to a series of laboratory tests, physicians should perform a screening for viral, genetic, and autoimmune causes of liver disease.

Non-invasive imaging methods like abdominal ultrasound, computed tomography, magnetic resonance imaging, and proton magnetic resonance spectroscopy may be used to diagnose MASLD, but not steatohepatitis and fibrosis [3]. Liver infiltrated by fat droplets has increased echogenicity (increased brightness) and vascular blurring on ultrasound imaging [18, 19]. The most accurate technique to detect and characterize hepatic steatosis is an unenhanced computed tomography scan (CT) which uses the difference between liver and spleen attenuation values. However, to diagnose MASLD is recommended both pre- and post-contrast enhanced computed tomography imaging. The contrast-enhanced computed tomography scanning allows for quantitative diagnosis of hepatic steatosis [18]. In the literature, there is information that magnetic resonance imaging (MRI), including magnetic resonance spectroscopy, can detect the presence of hepatic fat greater than 5.56% and it is worth reminding, that the defining threshold for steatosis is 5% [19].

However, non-invasive imaging for diagnosing advanced stages, steatohepatitis, and fibrosis, stayed limited. For this purpose, are used elastography and magnetic resonance elastography (MRE). During the diagnosing process is also used liver biopsy which allows to distinguish MASLD from metabolic dysfunction-associated steatohepatitis (MASH) [20].

### **Recognition**

For the whole patient with hepatic steatosis is intended an overarching term "steatotic liver disease" (SLD) [21]. In 2023, according to the multi-society Delphi consensus, which was established by an international panel led by the American Association for the Study of Liver

Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asociación Latinoamericana para el Estudio del Hígado (ALEH) the nomenclature of NAFLD was changed to MASLD, with corresponding changes in the classification and definition of the disease [21, 22]. For the first time, the disease is now defined not as a lack of other steatosis causes but by cardiometabolic criteria [22]. MASLD should be recognized in adults, who have demonstration of hepatic steatosis by imaging, histology, or prediction scores and have at least one of five risk factors [21, 22]. These cardiometabolic criteria are:

- 1) body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> or waist circumference  $> 94$  cm (male) and 80 cm (female) or ethnicity adjusted,
- 2) fasting serum glucose  $\geq 5.6$  mmol/l (100 mg/dl) or 2-hour post-load glucose levels  $\geq 7.8$  mmol/l ( $\geq 140$  mg/dl) or HbA1c  $\geq 5.7\%$  (39 mmol/l) or type 2 diabetes or treatment for type 2 diabetes,
- 3) blood pressure  $\geq 130/85$  mmHg or specific antihypertensive drug treatment,
- 4) plasma triglycerides  $\geq 1.70$  mmol/l (150 mg/dl) or lipid-lowering treatment,
- 5) plasma HDL-cholesterol  $\leq 1.0$  mmol/l (40 mg/dl) (male) and  $\leq 1.3$  mmol/l (50 mg/dl) (female) or lipid-lowering treatment [22].

Moderate alcohol consumption (up to 60 g per day in men and 50 g per day in women) by patients does not exclude diagnosis of MASLD [21]. For individuals who fulfill MASLD criteria, but additionally consume greater amounts of alcohol was selected the term metabolic dysfunction and alcohol-associated liver disease (MetALS) [21, 22]. In some cases, MASLD can co-exist with other liver diseases such as chronic viral hepatitis, autoimmune liver disease, and alpha-1-antitrypsin deficiency. The recognition of the contribution of MASLD in cases, when SLD is caused by multiple etiologies likely will have a big impact in terms of clinical practice [21].

The majority of MASLD is diagnosed in overweight and obese patients, but the disease can develop also in lean persons. The lean individual is defined as a person with a body mass index (BMI)  $< 25$  kg/m<sup>2</sup> in Western populations and  $< 23$  kg/m<sup>2</sup> in Asians. It is estimated that around 15% of MASLD cases worldwide occur among lean patients [23]. The literature suggests dividing MASLD in lean individuals into two subtypes:

- Type 1 is for patients with visceral adiposity and insulin resistance but normal BMI, and they can have common genetic variants, such as *PNPLA3* and *TM6SF2*.
- Type 2 is reserved for patients with disease driven by rare genetic variants, so in this case, individuals need genetic evaluation to unveil a monogenic disorder [23, 24].

## **Progression and complications**

The severe form of MASLD is MASH (metabolic dysfunction-associated steatohepatitis), which is characterized by the presence of liver inflammation and hepatocyte injury (ballooning) due to fat accumulation [25]. To make a MASH diagnosis a liver biopsy is still necessary. Based on histological features can be assessed the MASLD activity score (NAS). A diagnosis of MASH highly correlates with a NAS of  $\geq 5$  [26]. MASH can progress to advanced fibrosis and may be responsible for cirrhosis [27]. It is estimated that progress to cirrhosis occurs in about 22% of patients with MASH-related fibrosis [26]. Disease progression depends on the balance between pro-fibrogenic mechanisms and defense/repair mechanisms. Fibrosis is driven by upstream processes of damage and inflammation [28]. Patients with MASH and cirrhosis are at risk of complications of portal hypertension and hepatocellular carcinoma (HCC) [27]. Progression to HCC comes in about 2% of cases [26].

It is well-known that MASLD not only leads to end-stage liver disease but also has clinical implications on extrahepatic tissues with reduced quality of life. Emerging evidence suggests that MASLD contributes independently to cardiovascular disease (CVD) development. Furthermore, the most common causes of death in patients with NAFLD are CVD [28]. Research by Björkström et al. showed that patients with MASLD have not only a higher risk of HCC but also an increased risk for other cancers like colorectal cancer in men, and bladder, kidney, and uterine cancer [29].

## **Lifestyle interventions**

Lifestyle modifications are considered the first-line therapeutic option, particularly, in patients with MASH [30]. The literature indicates that a combination of lifestyle adjustments like weight loss, increasing physical activity, and smoking/alcohol cessation can be beneficial [31]. The most common dietary intervention treatment strategy for MASLD is caloric restriction (CR) [32]. Patients should avoid food with a high glycaemic index [31]. It is fully recommended to significantly reduce in consumption of saturated fatty acids, total fat, trans-fatty acids, and fructose. Sugar-containing soft drinks or juices are a source of fructose and fructose-rich diets are known to impair insulin sensitivity [30]. On the other hand, recommended increased consumption of monounsaturated fatty acids, omega-3 fatty acids, fibers, and specific protein sources such as fish and poultry [31]. The diet should be rich in fruits and vegetables. Plants and plant-based natural products are sustainable antioxidant sources containing biologically active compounds such as phenolic compounds and vitamins [30]. The most recommended dietary pattern in MASLD is a Mediterranean diet, which may reduce liver fat even without patients' weight loss. However, the Mediterranean diet involves moderate consumption of wine



and it is unclear whether patients with liver disease can adopt this recommendation. Research by Romero-Gómez et al. pointed out that NASH patients with cirrhosis should avoid alcohol, as any regular alcohol consumption puts them at a greater risk of developing HCC [33].

The beneficial role of caffeine is also emphasized [31, 33-34]. In the literature, it is suggested that regular coffee consumption can impact the liver and reduce hepatic enzymes (gamma-glutamyl transpeptidase, ALT), and its intake is associated with reduced hepatic fibrosis in MASLD patients. It is worth noticing, that regular coffee consumption was defined as the ingestion of caffeine only from regular coffee, not including other caffeinated beverages such as tea or sodas [34]. Caffeine is a strong antioxidant and can help reduce the burden of oxidative stress and inflammation in the liver which may translate to hepatoprotective effect [31]. These effects of coffee may be linked not only to caffeine but also to its polyphenolic fraction [33].

Regular physical activity can effectively treat MASLD in both non-obese and obese patients. A helpful role in treatment is resistance exercise and aerobic exercise. Moreover, a combination of these types of exercises is more reasonable and effective in clinical practice [32]. Aerobic exercise enhances the activity and expression of antioxidant enzymes [30]. It is proven that a 12-week course of resistance exercise can prevent MASLD progression and a 12-week course of aerobic exercise intervention may improve the status of patients with liver fibrosis [32]. However, if patients do not continue to exercise, the benefits from increased physical activity will be lost. It should be noted that genetic factors may affect patients' responses to physical activity. For example, *PNPLA3* seems to impact on lifestyle intervention. Individuals bearing unfavorable genotype GG respond better than patients with genotype CC or CG [33].

For most patients with MASLD, the primary treatment is weight loss. The results of weight reduction include improved liver biochemical tests and quality of life in patients with MASLD [31]. Most studies conclude that at least 7–10% of weight loss is required to induce an improvement in MASLD activity score (NAS) and its components (steatosis, lobular inflammation, and ballooning) [33]. Above 10 % weight loss is necessary to induce significant improvements in the liver histology of obese and overweight patients with MASH [30]. Despite all, even a mild reduction of weight like a loss of about 5% of initial body weight can result in reduced steatosis, lowering liver enzyme levels, and bring health benefits as clinically meaningful reductions in triglycerides, blood glucose, and glycated haemoglobin (HbA1c) [33].

### **Role of vitamins**

Vitamin E is a fat-soluble antioxidant that prevents the propagation of free radicals [35]. Its beneficial role also comes from anti-inflammatory, and anti-apoptotic properties [36]. A meta-analysis by Vadarlis et al. confirmed that intake of vitamin E compared with placebo was more

beneficial in reducing the values of transaminase levels in patients with MASLD as well as in patients with biopsy-proven MASH [37]. Additionally, in adults with NASH, vitamin E also reduced hepatic fibrosis [36]. However, the optimal duration of curative treatment is not known [37]. The safety of long-term vitamin E supplementation is an important issue because potential side effects are possible. The literature indicates the possibility of a connection between vitamin E treatment and a minor increase in the risk of prostate cancer or hemorrhagic stroke [35, 36]. There is conflicting data regarding dose safety. While one analysis noted that doses greater than 400 IU per day may be associated with increased all-cause mortality, another one reported that vitamin E below 5500 IU per day does not affect all-cause mortality [36]. To conclude, vitamin E could be considered as a treatment option in patients with MASLD and MASH [37]. The role of other vitamins is also of interest to researchers. Similar to vitamin E, vitamin C is also a strong antioxidant and thus can decrease the oxidative stress seen in individuals with MASLD and MASH. Among patients with MASLD and MASH, a common is vitamin D deficiency. However, data on the effectiveness of vitamin D supplementation in this disease has been unclear [36].

### **Pharmacological treatment**

Pharmacological therapy can be considered based on:

- 1) elevated fibrosis-4 index (FIB4) >1.3,
- 2) elevated serum aminotransferase level,
- 3) imaging such as transient elastography and magnetic resonance elastography,
- 4) plasma biomarkers for liver fibrosis such as the enhanced liver fibrosis test [38].

The current drug therapies are mainly focused on MASLD pathogenic factors, and as targets are also identify related metabolic disorders.

Generally, the antidiabetic drugs used to alleviate MASLD have certain clinical effects. Thiazolidinediones act as peroxisome proliferator-activated receptor PPAR- $\gamma$  agonists [32]. Pioglitazone treatment can counteract insulin resistance, modulate lipid and glucose metabolism, diminish hepatic and gastrointestinal inflammation, and induce significant modifications in body fat distribution [39]. However, clinical use of pioglitazone has documented side effects like increased risks of prostate or pancreas cancer, body weight gain, fluid retention, bone fracture in women, and increased cardiovascular events [40].

Glucagon-like peptide-1 (GLP1) is an intestinal hormone which is released in response to food consumption. On the market are available synthetic analogs of GLP1 receptor agonists (GLP1-RA) like liraglutide, semaglutide, dulaglutide, and exenatide [32]. GLP1-RA works through glucose-dependent stimulation of insulin secretion, inhibition of glucagon secretion, appetite

reduction, and slowing of gastric emptying [39]. The literature suggested that their effects on liver fat and inflammation are mediated by their favorable metabolic and weight-related actions [40]. Additionally, it is proven that GLP1-RA is efficacy and safe to reverse MASH [38].

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are well-known for cardiorenal protection. These drugs may be used as adjunctive pharmacological therapy among people with type 2 diabetes mellitus and MASLD [38]. SGLT2i mitigates oxidative stress [39]. Moreover, their beneficial effects include the reduction of hepatic triglyceride contents and serum aminotransferase levels [38]. SGLT2i may provide a valuable component of MASH combinational drug treatments [41].

As previously mentioned, CVD is the leading cause of death in patients with MASLD, thus one of the treatment targets is CVD risk reduction [38]. Among lipid-lowering drugs common are statins [32]. Statins are the first-line dyslipidemia therapy acting by lowering low-density lipoprotein (LDL) cholesterol and reducing high-risk atherosclerotic plaques [38]. However, these drugs should be avoided in decompensated cirrhosis [40]. A second line of dyslipidemia treatment can be used ezetimibe or it can be added to statin if the target cholesterol level is not achieved on maximal tolerated statin dose [38]. The literature pointed out that elevated blood pressure is associated with the progression of disease and fibrosis [32]. Lowering blood pressure by using antihypertensive drugs is also important to reduce CVD risk [38].

Ursodeoxycholic acid (UDCA) has anti-oxidative activity and exhibits anti-inflammatory effects [32, 40]. As research showed high-dose UDCA treatment for 12 months may reduce hepatic aminotransferase levels in MASH patients and improve glycemic control and insulin resistance [32]. Also, there are several specific liver-targeting agents. Resmetirom and other thyroid hormone receptors subtype  $\beta$  agonists, fibroblast growth factor 21 analogs, and lanifibranor are under clinical trials [39]. The combination of liver-targeted drugs like resmetirom with antihyperglycemic and/or weight-reducing drugs may improve therapy effectiveness and reduce the required used drug dose [41].

## **Conclusion**

MASLD should be diagnosed in patients with liver steatosis who additionally meet at least 1 of 5 cardiometabolic criteria. Treatment should start with lifestyle changes. Patients should be encouraged to adjust their diet, increase their physical activity levels, and lose weight. The approach to the disease also aims to reduce CVD risk factors, including through pharmacotherapy. Furthermore, research into new treatment strategies is ongoing.

### **Author's contributions**

Conceptualization: Adrian Kruszewski, Anna Dąbrowska; methodology: Adrian Kruszewski, Natalia Paduszyńska; check: Paulina Przybysz, Maja Kucharska, Monika Szyszka; formal analysis: Karolina Błaszczak; investigation: Anna Dąbrowska, Natalia Paduszyńska; resources: Maja Kucharska, data curation: Monika Szyszka, Paulina Przybysz; writing-rough preparation: Anna Dąbrowska, Karolina Błaszczak, Natalia Paduszyńska; writing-review and editing: Adrian Kruszewski, Paulina Przybysz, Karolina Błaszczak; visualization: Monika Szyszka, Maja Kucharska; supervision: Adrian Kruszewski, project administration: Adrian Kruszewski  
All authors have read and agreed with the published version of the manuscript.

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The authors report no conflict of interest.

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