Current Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the new term chosen to replace non-alcoholic fatty liver disease (NAFLD). It is characterized by hepatic steatosis in the absence of other causes of liver fat accumulation. The prevalence of MASLD is increasing and now among top causes of hepatocellular carcinoma. The presence of hepatic steatosis with the finding of any of a cardiometabolic risk factor (CMRF) will confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. There are currently no specific drugs for therapy of MASLD. Current mainstay for management of MASLD is lifestyle interventions focused around weight loss. Lifestyle interventions can be done by dietary modification or increasing physical activity level. Pioglitazone and vitamin E are only recommended for patient whom was confirmed MASLD by liver biopsy. New agents such as obeticholic acid, elafibranor, selonsertib, and cenicriviroc are still waiting for phase III result to be recommended as therapy for MASLD. Bariatric surgery can be advised for MASLD patient with obesity who is not adequately controlled by medical therapy.

Keywords: *metabolic, steatosis, management, lifestyle, drugs*

ABSTRAK

Metabolic dysfunction-associated steatotic liver disease (MASLD) merupakan istilah baru yang ditetapkan untuk menggantikan non-alcoholic fatty liver disease (NAFLD). Penyakit ini disebabkan karena akumulasi lemak di hati (steatosis) tanpa adanya penyebab sekunder dari akumulasi lemak tersebut. Prevalensi MASLD di seluruh dunia terus meningkat dan menjadi salah satu penyebab terbanyak dari kanker hati. Diagnosis MASLD saat ini ditegakkan melalui kondisi steatosis hati disertai minimal satu dari lima faktor risiko kardiometabolik. Tatalaksana spesifik untuk MASLD belum ditemukan hingga saat ini. Tatalaksana MASLD berpusat pada perubahan pola hidup dengan fokus penurunan berat badan. Perubahan pola hidup dapat dilakukan dengan perubahan diet dan peningkatan aktivitas tubuh. Pioglitazone dan vitamin E saat ini hanya direkomendasikan sebagai terapi MASLD yang telah terbukti secara biopsi. Beberapa obat seperti asam obetikolat, elefibranor, selonsertib dan cenicriviroc masih menantikan hasil penelitian fase III untuk dapat direkomendasikan sebagai terapi MASLD. Operasi bariatrik dapat dilakukan pada pasien MASLD dengan obesitas yang gagal diobati dengan terapi medikamentosa.

Kata kunci: *metabolik, steatosis, tatalaksana, pola hidup, obat*

INTRODUCTION

The term non-alcoholic fatty liver disease (NAFLD), while it's widely used, has always been appreciated that it did not accurately capture what the etiology of the disease was. The term "non-alcoholic" and "fatty" have been considered to be stigmatizing by some. These concerns led to a multi-stakeholder effort under the auspices of the American Association for Study of Liver Disease (AASLD) and the European Association for Study of the Liver (EASL) in collaboration with the Asociacion Latinoamericana para el Estudio del Higado (ALEH) with engagement of academic professionals from around the world to develop a consensus on a change in nomenclature and the diagnosis criteria for the condition, which was announced in June 2023. Steatotic liver disease (SLD) was chosen as an overarching term to encompass the various etiologies of steatosis. The name chosen to replace NAFLD was metabolic dysfunction-associated steatotic liver disease (MASLD). There was consensus to change the definition to include the presence of at least one of five cardiometabolic risk factors (CMRF). MASLD is defined as the presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause. Another category, outside MASLD, termed MetALD was selected to describe those with MASLD who consume greater amounts of alcohol per week (140 g/week and 210 g/week for females and males respectively). Metabolic dysfunction-associated steatohepatitis (MASH) is the replacement term for non-alcoholic steatohepatitis (NASH).[1]

Fat droplets in more than 5% of the liver cells is considered as abnormal or pathological. In many cases, the extra fat in the liver cells does not seem to be harmful or affect how the liver works. When the liver cells containing fat droplets become inflamed and damaged, it is called steatohepatitis. The inflammation can lead to fibrosis, with scar tissue forming inside the liver. This fibrosis can lead to cirrhosis and then liver cancer.[2]

There are currently no medicines approved by U.S. Food and Drug Administration to specifically treat MASLD.[2] The cornerstone of MASLD treatment right now are healthy diet and weight loss, however, some diabetes and anti-obesity medications can be beneficial.[2] Bariatric surgery is also effective for weight loss and reducing liver fat in person with severe obesity.[2] This article will concentrate on the current progress of management of MASLD (non-pharmacologic and pharmacologic).

EPIDEMIOLOGY

Non-alcoholic fatty liver disease (NAFLD), now known as metabolic dysfunction-associated steatotic liver disease (MASLD), is the most common cause of chronic liver disease affecting 25% of the global population.[2] The highest prevalence rates for MASLD have been reported from the Middle Eastern countries. In addition, the prevalence rates are significantly higher in those with type 2 diabetes mellitus (T2DM) and obesity. In fact, among those with obesity, the prevalence of MASLD is between 25–30%, while approximately 30% to 40% of persons with diabetes have MASLD.[2,3] Twelve to 14% of persons with MASLD have a more aggressive form known as metabolic dysfunction-associated steatohepatitis

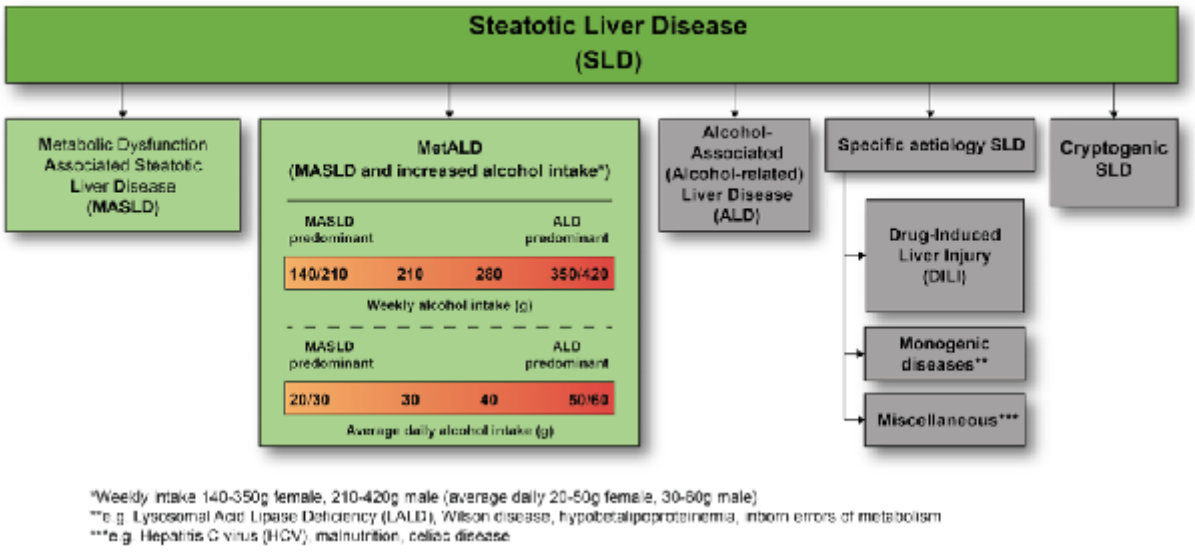

Figure 1. Steatotic liver disease spectrum[1]

(MASH), which can progress to advanced liver fibrosis, cirrhosis, or liver cancer.[2] MASH is now among the top causes of hepatocellular carcinoma (HCC) and the second most common cause of HCC in those on the waiting list for liver transplantation in the United States after hepatitis C.[3]

DIAGNOSIS

Patient with risk factors like obesity, pre-diabetes, T2DM, and or metabolic syndrome should be screened for MASLD.[2,4] Liver biopsy was once required for the definitive diagnosis for NAFLD.[5] In the past, the definition of NAFLD is based on the presence of hepatic steatosis in > 5% of hepatocytes in the absence of other causes of liver fat accumulation.[6] At the present, the presence of hepatic steatosis with the finding of any of a cardiometabolic risk factor (CMRF) would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, then this is consistent with a combination etiology. In the case of alcohol this is term MetALD. In the absence of overt cardiometabolic criteria, other etiologies must be excluded and if none is identified, this is termed cryptogenic SLD, although depending on clinical judgment could also be deemed to be possible MASLD and thus would benefit from periodic reassessment on a case by case basis.[1]

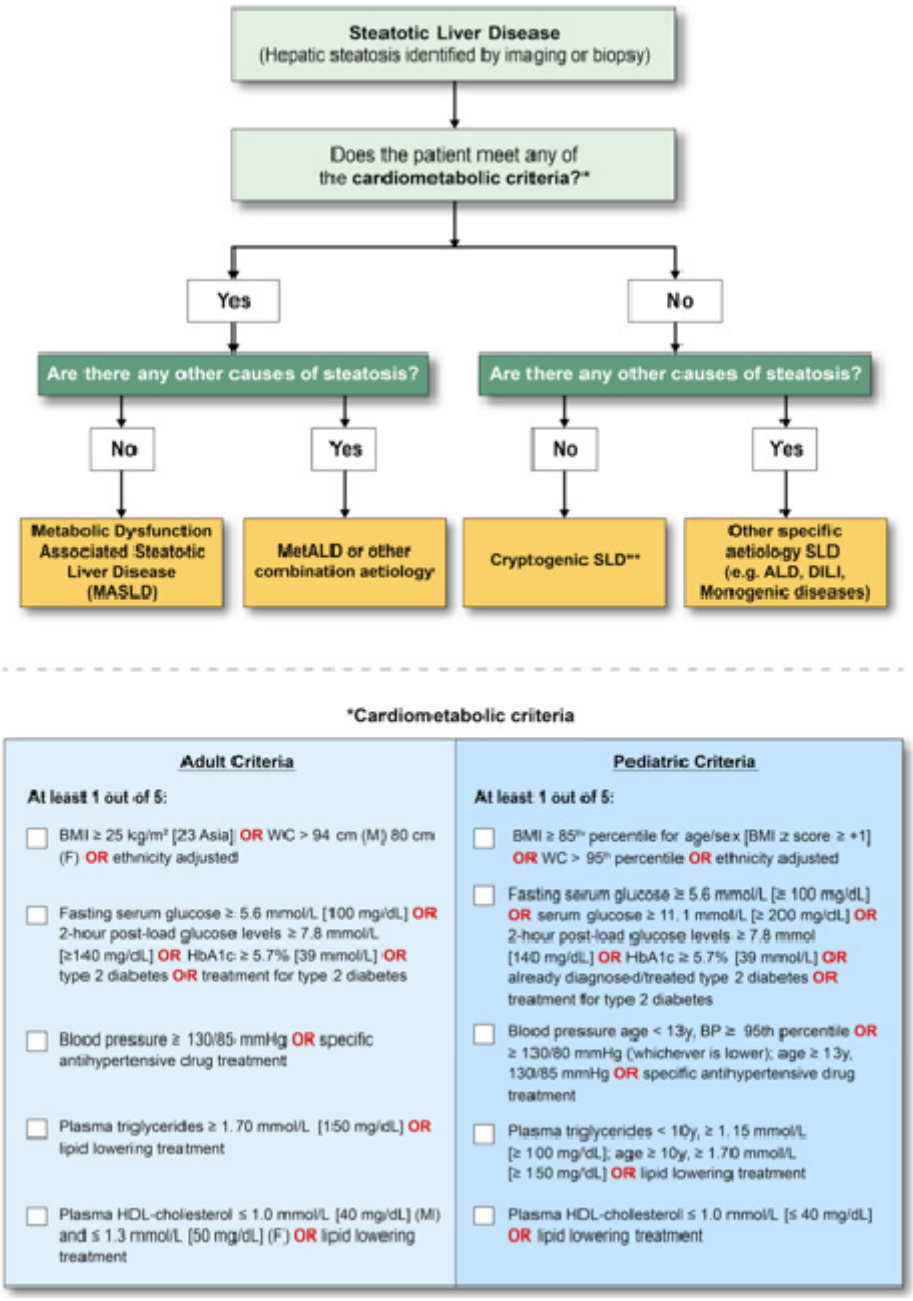

Figure 2. MASLD diagnostic criteria[1]

NON-PHARMACOLOGIC MANAGEMENT

There are currently no specific drugs for the treatment of MASLD. The combination of weight loss, dietary change, and increased physical activity are the mainstay of the management of MASLD. That combination can be helpful in reducing liver fat and inflammation. It is also effective in reducing the risk for T2DM, cardiovascular disease, and HCC.[2]

Research has shown that weight loss is an effective treatment for MASLD. Weight reduction, whichever way it is achieved, leads to improvement in liver blood test (liver enzymes), the amount of liver fat and liver inflammation, as well as the amount of scar tissue or fibrosis. The impact of weight loss on liver improvement depends on the degree of weight reduction. A weight reduction of > 5% is usually able to reduce liver fat, 7–10% can improve liver inflammation, and > 10% can improve fibrosis/scarring. The guideline written by three scientific societies (European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO)) recommends a weight loss target of 7–10% for overweight or obese patient with MASLD.[2,7]

Saturated fat has been shown in several studies that it has a reinforcing effect on liver fat accumulation. High saturated fat food markedly increases liver fat, liver blood tests (liver enzymes), and serum lipids. Foods rich in saturated fat were found mostly in processed food, butter, and high-fat dairy products. They are also included in high-fat meat (e.g. internal organs like liver, brain, and processed meats like sausages), cakes, cookies, ice cream, and other sweets. Reduce the amount of processed food can be helpful in managing MASLD.[2,8]

There are two type of sugars that is natural sugar and added sugar. Natural sugar refers to the sugar that is an integral constituent of whole fruit, vegetable, and milk products. Meanwhile, added sugar refers to sucrose (table sugar) or other refined sugars (fructose and high-fructose corn syrup) that was added into food, fruit drinks, and other beverages. Many studies showed an association between added sugars and MASLD, which is more prominent if it is in the form of sugar-sweetened beverages. Among children and adolescents, fructose consumption was independently associated with MASH. Importantly, reducing sugar consumption in children led to an improvement in liver fat within a few weeks. These findings imply that the intake of sugar-sweetened beverages and foods with high added sugar should be reduced as part of the treatment of MASLD.[2,9,10]

Adequate consumption of fruits and vegetables may reduce the risk of MASLD because they contain of fiber, vitamins, and non-vitamin antioxidants (such as phenolic compounds). Studies indicated that dietary intake of vitamin E and C and phenolic compounds might protect against MASLD-related liver damge. The best sources of vitamin E and C are nuts, seeds, plant oils, fruits, and vegetables. Phenolic compounds are abundantly present in foods such as berries, nuts, coffee, tea, and whole grains.[2,11]

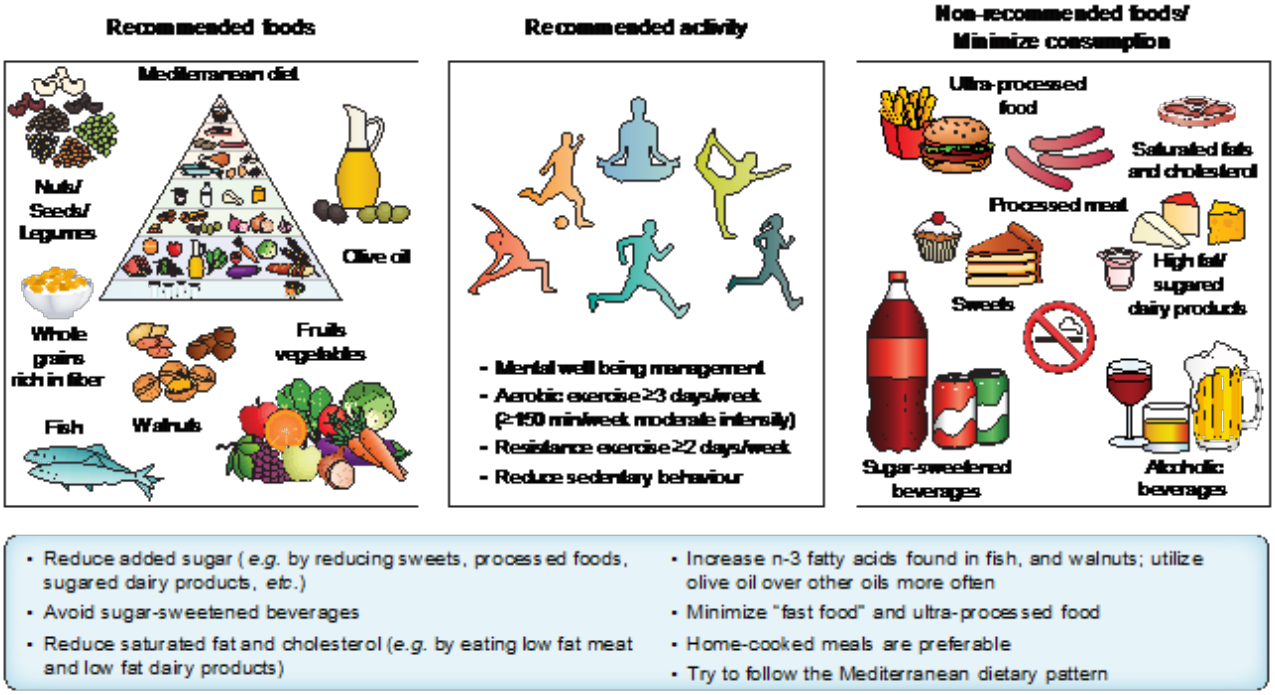

Figure 3. Non-pharmacologic management of MASLD[2]

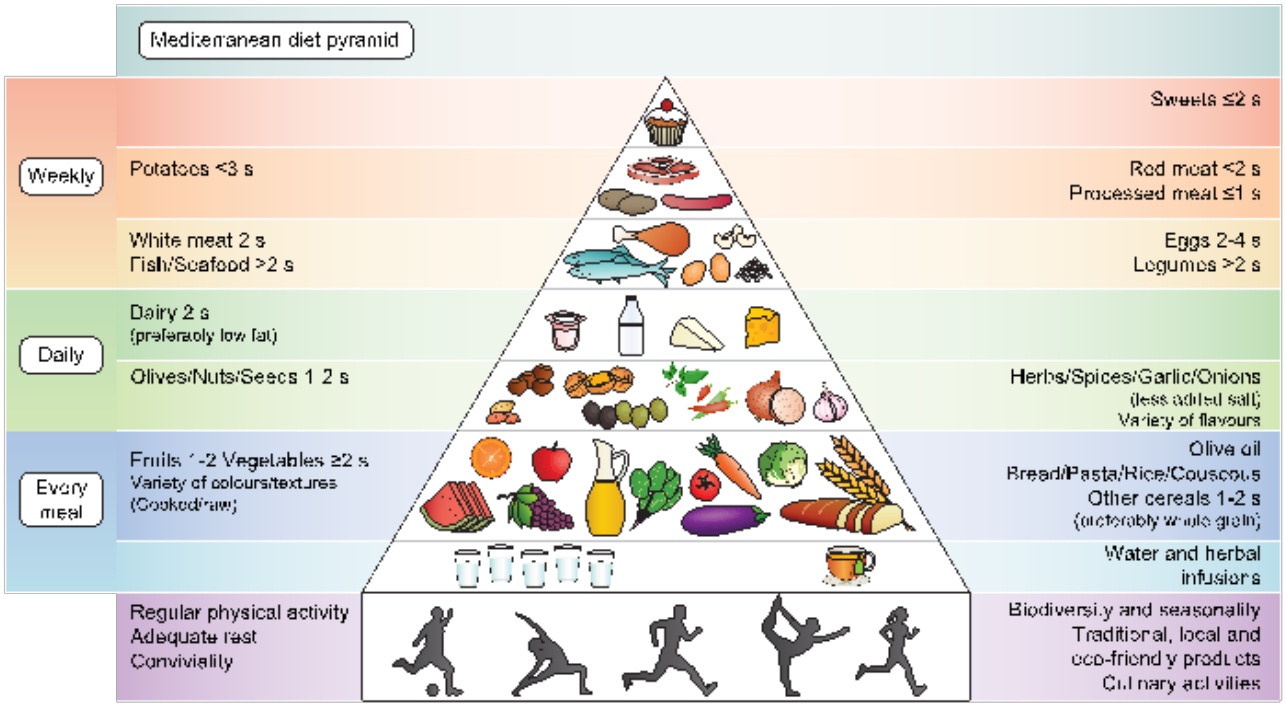

Figure 4. Mediterranean diet[2]

The traditional Mediterranean diet is the most studied dietary patterns. This diet is characterized by a high intake of olive oil, vegetables, fruits, nuts, legumes, whole grains, fish, and seafood. It is also characterized by a low intake of red meat and processed foods. Importantly, the Mediterranean diet is also characterized by reduced sugars and refined carbohydrates, minimizing processed or "fast foods" and to have more home-cooked meals. Several studies have shown a harmful association between high meat intake and MASLD, specifically red meat (such as beef, lamb, and pork) and processed meat (such as hamburger, salami, sausages, and processed schnitzel). In two interventional studies, two months of a Mediterranean diet led to a significant decrease in liver fat independent of any weight loss. For this reason, the Mediterranean diet has been recommended for the treatment of MASLD by EASL-EASD-EASO.[8,12]

Sedentary behaviors are common in MASLD.[2] Ministry of Health of Republic of Indonesia defines sedentary lifestyle as any waking activities characterized by a low level of energy expenditure (e.g. watching television, using a computer, traveling by car or bus).[13] A 1.15% increase in liver fat was associated with each additional hour of time spent sedentarily per day.[2] Population-based studies have shown that physical activity is effective in reducing liver fat. It is also effective in reducing the risk of other comorbid metabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and obesity. There are two types of exercise: aerobic exercise (cardio) and resistance exercise. Aerobic exercise strengthens the heart and lungs and also improves the way body uses oxygen. It normally uses the large muscle groups, is rhythmic in nature, and can be maintained for at least 10 minutes. Examples include brisk walking, swimming, cycling, and dancing. Meanwhile, resistance exercise strengthens the muscles and improves muscle tone and bulk. It includes any exercise where the muscles contract against a force and can include lifting weights, use of resistance bands, or pushing against body weight. A combination of aerobic and resistance exercise provides the greatest health benefits.[14,15]

Guidelines recommend over 150 min/week of moderate intensity physical activity over 3–5 sessions including a combination of aerobic and resistance training. The effects on liver fat follow a volume-response relationship: higher volumes of physical activity/exercise are also associated with greater weight loss and systematic improvement of comorbidities. Ultimately, physical activity/exercise program needs to be matched with patient needs and preferences, taking into account patient baseline fitness and other health conditions.[14,16]

PHARMACOLOGIC MANAGEMENT

Despite intensive research and investment by drug companies, there are currently no specific drugs that were approved by regulatory agencies for the

treatment of MASLD. Treating all the metabolic factors associated with MASLD and trying to improve MASLD using lifestyle modifications described, are recommended to any patient regardless of disease severity. When it comes to the question of starting specific drug treatment for MASLD, the current consensus is that this is indicated in patients with MASH, particularly in those with more disease activity and with some scar tissue. When there is no biopsy, other modalities, such as liver stiffness, USG, or MRI can be used as a guidance to start therapy. Currently there is no single set of criteria that are agreed upon worldwide, and so many different (sets of) test criteria are in use.[2,3,6]

PIOGLITAZONE

Several studies and a meta-analysis have consistently demonstrated an improvement in liver blood tests and in liver biopsy features following pioglitazone administration at doses 30–45 mg/day vs. placebo, irrespective of the presence of T2DM. In the PIVENS trial, pioglitazone was compared with placebo and vitamin E. Pioglitazone significantly reduced liver blood tests, steatosis, and liver cell damage and inflammation. Pioglitazone (45 mg/day) was particularly effective for the treatment of MASH in patients with pre-diabetes or T2DM. The body weight increase induced by pioglitazone needs further discussion. It may seem contradictory that losing weight can improve the condition of the liver, while a drug that increases weight can also have positive effect on the liver. This can be explained by the balance between the calorie overload and the capacity of the fat tissue to handle this. If the calorie overload exceeds the storing capabilities of the fat, the fat tissue gets inflamed and dysfunctional. As a consequence, a fat releases substances that damage other organs and forces the fat to go elsewhere, including the liver. Reducing weight by lifestyle modification is one way to tackle this problem. Another way, which is what pioglitazone does, is to improve fat tissue function. Thanks to this effect of the drug, the "good" fat tissue, meaning the subcutaneous fat tissue, can expand. This allows fat to shift from the abdominal fat and other body areas to subcutaneous fat. The expansion of the subcutaneous fat leads to weight gain. This weight gain is in this case a translation of metabolic improvement and goes along with improving, and not worsening liver lesions.[2,17]

VITAMIN E

Vitamin E has anti-cell death and antioxidant properties, therefore, it has been proposed for the treatment of MASLD. In the PIVENS trial at the dose of 800 international units (IU)/day, vitamin E was significantly better than placebo at improving steatohepatitis, but it had no significant effects on fibrosis. American Association for the Study of Liver Disease (AASLD) guideline recommends vitamin E to be indicated in patient with MASH who are biopsy-proven without the presence of T2DM and or cirrhosis. A very recent study concluded that only a combination therapy of vitamin E (800 IU/day) and pioglitazone (45 mg/day) achieved the most challenging targets of reducing liver cell damage and inflammation. However, the fibrosis did not improve.[17,18]

GLUCAGON-LIKE PEPTIDE RECEPTOR AGONISTS (GLP-1 RA)

Glucagon is an important hormone in the regulation of energy handling in your body. GLP-1 RA are a class of drugs that improve control of your blood sugar, cause weight loss and improve blood lipids. They are approved for the treatment of diabetes and obesity. Liraglutide is one of these GLP-1 RA and has been tested at a daily dose of 1.8 mg in a small 1-year study. MASH resolved significantly more frequently in liraglutide-treated patients than placebo-treated patients. Treatment with liraglutide also led to a trend in improvement of fibrosis stage. The same holds true for semaglutide, which was already shown to improve liver blood tests in patients with T2DM and obesity. Semaglutide was tested at several dose regimens for a treatment period of 1.5 years. MASH resolved significantly more frequently in patients treated with the higher doses of semaglutide than in patients that received placebo. [2,19,20]

OTHER AGENTS

Several pharmaceutical agents, including obeticholic acid (OCA), elafibranor, selonsertib, and cenicriviroc are currently in phase III of randomized controlled trials to assess their potential roe in the management of MASLD. OCA activates the farnesoid X nuclear receptor in the liver, leading to improved hepatic insulin sensitivity and decreased gluconeogenesis, inflammation, lipogenesis, and fibrosis. Unfortunately, with treatment there is a rapid rise in low-density lipoprotein cholesterol, and although this side effect can be treated effectively with

statin medication, the cardiovascular consequences of OCA treatment are unknown. Elafibranor is an agonist of peroxisome proliferator-activator receptor alpha (PPARα) and PPARδ. Elafibranor improves insulin sensitivity and reduce hepatic inflammation in mouse models. Selonsertib acts to inhibit apoptosis signal-regulating kinase 1, which is involved in hepatocyte apoptosis and fibrosis. During the phase II trial, patients receiving selonsertib demonstrated improvements in several measures of liver disease severity, including fibrosis stage and liver fat content. Cenicriviroc, a C-C motif chemokine receptor 2/5 antagonist, reduces inflammation, has antifibrosis effects and improves insulin sensitivity.[6]

BARIATRIC SURGERY

Bariatric surgery effectively achieves weight loss and weight loss maintenance in patients with obesity. The effect of bariatric surgery on body weight largely exceeds the 10% weight loss target associated with liver fat clearance, MASH resolution and fibrosis reversal. The agreed criteria for the surgical management of obesity and metabolic disorders (body mass index (BMI) ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with complicating disorders, with no resolution after medical treatment) are also applicable for MASLD. Laparoscopic Roux-en-Y-gastric bypass and sleeve gastrectomy are the most performed surgical procedures.[2,21]

CONCLUSION

Prevalence rate of MASLD keeps increasing alongside obesity. Patient with MASLD has increased risk of morbidity and mortality caused by cardiovascular disease and T2DM. Lifestyle intervention focused on weight loss is the mainstay in MASLD management. Pioglitazone and vitamin E are only recommended for patient whom MASLD confirmed by liver biopsy. Some anti diabetic agents like SGLT2 inhibitor or GLP-1 RA has shown promised result but still waiting further trials before they can be recommended as MASLD therapy. New agents such as obeticholic acid, elafibranor, selonsertib and cenicriviroc are still waiting for phase III result to be recommended as therapy for MASLD. Bariatric surgery can be advised for MASLD patient with obesity who is not adequately controlled by medical therapy.

Table 1. Selected pharmacological treatments in the treatment of MASH[6]

	Mechanism of action	Benefit	Indications	Limitations and side effects
Pioglitazone	Reduce hepatic fatty acid uptake due to an increase uptake by adipocytes	- ↓ hepatic steatosis - ↓ inflammation - Improve glycaemic control	Biopsy-proven MASH with or without T2DM	- Weight gain - Increased risk of congestive heart failure
Vitamin E	Antioxidative, anti-inflammatory	- ↓ hepatic steatosis - ↓ inflammation - ↓aminotransferase levels	Biopsy-proven MASH with or without T2DM	Increased risk of haemorrhagic stroke and prostate cancer
Obeticholic acid	Improve hepatic insulin sensitivity, decrease gluconeogenesis	- ↓ inflammation - ↓ hepatic lipogenesis - Improve fibrosis	Not currently recommended to treat MASLD	- Raises LDL-C - Pruritus - Result from phase III trial awaited (REGENERATE)
Elafibranor	Improve insulin sensitivity, anti inflammatory	- ↓ inflammation - Improve cardiometabolic risk factors	Not currently recommended to treat MASLD	Results from phase III trial awaited (RESOLVE-IT)
Selonsertib	Inhibit hepatocyte apoptosis, antifibrotic	- ↓ hepatic steatosis - Improve fibrosis	Not currently recommended to treat MASLD	Results from phase III trial awaited (STELLAR 4)
Cenicriviroc	Antifibrotic, anti-inflammatory, improve insulin sensitivity	- Improve glycaemic control - Improve fibrosis	Not currently recommended to treat MASLD	- Asymptomatic rise in amylase - Results from phase III trial awaited (AURORA)
GLP-1 receptor agonist	Inhibit glucagon secretion, decrease hepatic glucose production, delay gastric emptying, promote satiety	- ↓ inflammation - ↓ steatosis - ↓ fibrosis - Weight loss - Improve glycaemic control	Not currently recommended to treat MASLD	- Gastrointestinal upset - Results from further trials awaited
SGLT2 inhibitor	Glucosuria, altered lipid metabolism	- Decrease aminotransferase levels - Weight loss - Improve glycaemic control	Not currently recommended to treat MASLD	Benefits only verified in small pilot studies

MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; T2DM: type 2 diabetes mellitus; LDL-C: low density lipoprotein-cholesterol; GLP-1: glucagon like peptide-1; SGLT2: sodium-glucose transport protein 2

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