Review Article

Non-Pharmacological and Pharmacological Approaches to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): An Update

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ABSTRACT

Recently, based on an international consensus, the term The term "non-alcoholic fatty liver disease" (NAFLD) was replaced by "metabolic dysfunction-associated steatotic liver disease" (MASLD). Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with obesity and type 2 diabetes mellitus. Lifestyle interventions aiming at substantial weight loss and pharmacological intervention to achieve desired histological outcomes are cornerstones of management of MASLD. Among pharmacological interventions, originally developed as antidiabetic drugs, incretin mimetics and SGLT2 inhibitors were found to reduce steatosis and fibrosis. Certain incretin agonists effectively improve histological features of MASLD. On the other hand, despite mild weight gain, one PPARã agonist (pioglitazone) was found to improve MASLD with certain benefit on fibrosis. Furthermore, benefits of other drug options, which directly target hepatic lipid metabolism (e.g., lipogenesis inhibitors, FGF21 analogs) have also been highlighted. Some combination therapies were also proved beneficial. Our discussion is based on weight loss, glycemic control, reductions of liver enzymes and histological improvement. We have compared results from clinical trials of different drugs as well as systematic review and meta analysis.

Keywords: *Metabolic dysfunction-associated steatotic liver disease, non-alcoholic fatty liver disease, obesity, weight loss*

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INTRODUCTION

Recently, based on an international consensus, the term The term "non-alcoholic fatty liver disease" (NAFLD) was replaced by "metabolic dysfunction-associated steatotic liver disease" (MASLD)[1]. MASLD requires the presence of steatosis and at least one cardiometabolic risk factor (overweight/obesity, hyperglycemia, hypertension, hypertriglyceridemia, or low high density lipoprotein cholesterol), in the absence of alcohol consumption. MASLD closely relates to obesity, insulin resistance and type 2 Diabetes, with which it shares many pathogenic features[2]. MASLD has been recognized as an important risk factor for several other diseases including hepatocellular carcinoma (HCC), extra-hepatic malignancies and chronic kidney disease[3]. Currently, MASLD affects about 25% of the world's adult population[4], while 29.62% in Asia[5]. Approximately, 10-20% of people with steatosis progress to "metabolic dysfunction-associated steatohepatitis" (MASH)[6]. The prevalence of MASH in the general population is projected to rise by 40% within 2030 in Europe[6]. Now-a-days, MASH/MASLD has evolved as one of the main reasons of

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liver transplantation in the developed countries of the world[7,8].

OBESITY, INSULIN RESISTANCE AND MASLD

In people with obesity, metabolic dysfunction-associated steatotic liver disease (MASLD) prevalence is estimated to be about 75%[9]. The first step in MASLD pathogenesis is adipose tissue dysfunction. With overweight and obesity, adipocytes need to cope with excessive nutrient delivery and storage, which is achieved by cellular hypertrophy. This adipocyte hypertrophy results in tissue hypoxia and mechanical stress, which trigger immune cell activation and invasion[9,10]. Consequently, insulin resistance develops, paralleled by altered adipokine (i.e., adiponectin, leptin etc.) secretions and impaired mitochondrial functions, further promoting adipose tissue inflammation[10-13]. Besides, evidence showed that visceral adiposity is associated with higher lipolysis, greater insulin resistance and increased release of pro-inflammatory and pro-fibrogenic mediators, which ultimately leads to visceral adipose tissue compartments also contribute to development and progression of MASLD[11-14]. It may explain the cause behind the fact that people of Asian ethnicity show higher visceral fat accumulation at a given BMI in comparison to with Caucasian people, which may explain the higher prevalence of MASLD in Asian population[15,16]. Evidence also showed that visceral adiposity correlates not only with insulin resistance of liver and adipose tissues but also with liver lipid content and the degree of liver fibrosis, both in obese and lean individuals[17]. The rate of hepatic de novo lipogenesis is much greater in MASLD, which further contributes to intrahepatic lipid accumulation[18]. With increasing hepatic lipid accumulation, there is generation of toxic lipid intermediates (diacylglycerols, ceramides) and altered hepatocellular mitochondrial respiration rates. These together drive hepatic insulin resistance, hepatocellular inflammation and oxidative stress - all of these fueling hepatic pro-fibrotic pathways[17,18].

NON-PHARMACOLOGICAL TREATMENT OF MASLD

Lifestyle interventions: Caloric restrictions can rapidly reduce steatosis and hepatic insulin resistance[19]. Histological improvement was observed in different MASLD components depending on the amount of weight loss. Only 5-7% of weight loss may lead to tremendous reduction in liver lipid content in patients having MASLD, while cent percent steatosis improvement and up to 65% MASH resolution (defined as the absence of hepatocellular ballooning) can be achieved after reducing 7-10% of body weight[20-22]. Therefore, healthy dietary habit is very relevant, for example, Mediterranean diets showed beneficial effects on liver lipid content[23,24]. These diets rely on plant-based foods. Despite their total fat content amounts to 30-40% of daily energy intake, the distinct fat composition with a higher monounsaturated-to-saturated fatty acid ratio contributes to lower liver lipid accumulation[25,26]. Other components, such as low intake of red meat and high intake of antioxidant polyphenols, may also mediate the beneficial effects of Mediterranean diets[25,26]. International guidelines endorsed by the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), European Society for Clinical Nutrition and Metabolism (ESPEN) also recommended Mediterranean diets for people with MASLD[27-29]. Meanwhile, recent evidence showed the beneficial effects of gradual weight loss as compared to rapid weight loss in regard to fat mass and basal metabolic rate[30]. It is noteworthy that for any lifestyle concept, it is essential to achieve loss of fat mass (FM) while maintaining lean body mass (LBM). Loss of LBM impedes sustainability of weight loss by causing low basal metabolic rate and slowing metabolic processes, which may result in regaining FM[31]. Besides, moderate physical exercise improves liver lipid content[32,33]. Nonetheless, a combination of diet restriction and exercise is more effective than each intervention alone[34].

PHARMACOLOGICAL TREATMENT OF MASLD

Drugs with weight loss-dependent effects for MASLD treatment: There is increasing evidence that pharmacologically-induced weight loss can also reduce liver lipid content. Apart from weight loss, those drug-elicited effects may contribute to the recovery of liver homeostasis.

1. **Incretin mimetics:** Incretin mimetics work by "mimicking" the actions of natural incretin hormones, which help lower blood sugar. Incretin based therapies can activate a single receptor or multiple receptors, e.g., GLP-1 receptor agonist drugs, drugs that stimulate GLP-1 and GIP receptors (dual agonists), and drugs that activate GLP-1, GIP, and glucagon receptors (triple agonists).

GLP-1 receptor agonists: In general, all GLP-1RAs or "Glucagon-like peptide-1 receptor agonists" (short-acting e.g., exenatide and long-acting e.g., liraglutide, semaglutide, albiglutide etc.) can induce weight loss by central GLP-1 receptor activation in specific regions in the hypothalamus, promoting satiety and decreasing appetite[35,36]. Importantly, GLP-1RAs reduce the risk of "major adverse cardiac events" (MACE) and improve kidney function in people with type 2 diabetes[37]. The primary mediator of the observed improvements in MASH by GLP-1RA treatment is presumably weight loss. Two different RCTs with liraglutide and semaglutide in mixed collectives of people with and without type 2 diabetes provided evidence of histological MASH resolution without worsening of fibrosis as compared to placebo. MASH resolution was mainly driven by improvements in steatosis and ballooning for liraglutide[38]; apart form that semaglutide reduced inflammation, too[39]. Thus, with liver-related effects as well as cardiovascular and renal benefits and the favorable safety profile, GLP-1RA should be considered for MASLD treatment, especially in obesity and type 2 diabetes[36,37].

Dual and Triple agonists: Tirzepatide (dual agonist) used in people with MASH showed significant weight loss along with histologic improvement in hepatic steatosis, as reflected through changes in different biomarkers[40,41]. Cotadutide and survodutide (dual agonists) were also found effective in MASH treatment in type 2 diabetic patients[42,43]. Retatrutide (triple agonist) treatment trial in MASLD showed liver fat reductions which were significantly related to changes in body weight, abdominal fat and metabolic measures associated with improved insulin sensitivity and lipid metabolism[44].

2. SGLT Inhibitors:

Several studies showed that sodium-glucose transport protein 2 (SGLT-2) inhibitors have effects on hyperglycemia and metabolic obesity, e.g., canagliflozin, dapagliflozin, empagliflozin and ipragliflozin were able to improve hepatic insulin sensitivity and insulin secretion and clearance; they also reduced body weight as well as liver fat in people with type 2 diabetes, with and without MASLD, compared with patients who received a placebo[45-48].

3. Metformin:

Metformin is associated with modest but consistent decrease in body weight, which was also found beneficial for MASLD components[49-52]. In MASLD, metformin may reduce steatosis on ultrasound and have a beneficial role in liver histology collated with insulin resistance improvement[51]. However, histological responses like reducing steatosis, inflammation, hepatocellular ballooning and fibrosis were found doubtful[52]. Although treatment with metformin could not improve liver enzymes, it improved lipid parameters and insulin metabolism regulation in pediatric patients[51].

Drugs for MASLD treatment with weight loss independent metabolic effects:

1. Peroxisome proliferator-activated receptor (PPAR) agonists: Due to their pivotal role in hepatic inflammation and fibrogenesis, distinct PPAR variants (α, δ, γ) have been identified as potential pharmacological targets to combat MASLD[12,53,54].

PPARα agonists: PPARα agonist action on lipid metabolism is driven by stimulation of hepatic fatty acid transport, lipolysis and peroxisomal as well as mitochondrial β-oxidation. However, pharmacologic targeting of PPARá did not suffice to reduce liver lipid content to a clinically relevant extent[53-55]; however. imaging showed decreased liver stiffness with pemafibrate (a PPARα agonist)[55].

PPARγ agonists: PPARγ is highly expressed in white adipose tissues and controls non-esterified fatty acid uptake, lipogenesis as well as reduces adipocyte tissue inflammation[54]. In patients with MASH, treatment with pioglitazone, one of the most prescribed PPARγ agonistic drug over decades, was found associated with histological improvements of liver including reversal of fibrosis[56,57], despite mild weight gain[57].

Dual/pan-PPAR agonists: The dual α/δ PPAR agonist like elafibranor and a pan-PPAR agonist like lanifibranor seem to be effective for MASLD treatment in terms of MASH resolution without worsening of fibrosis and/ fibrosis improvement[58,59].

2. Modulators of the mitochondrial pyruvate carrier: MSDC-0602K, a PPARγ-sparing pioglitazone derivative, was developed to target mitochondrial pyruvate carriers (MPC) 1 and 2, which ultimately led to significant glycemic control and reductions in liver enzymes and non-metabolic steatosis[60,61]. However, in patients with MASH and fibrosis, it failed to meet the predefined histological endpoints compared to placebo[61].

3. Fibroblast growth factor 21 (FGF21) analogues:
Improvements in dyslipidemia and MASLD have been repeatedly observed in treatment with efruxifermin and pegozafermin; histological endpoints suggested fibrosis regression in people with MASH-induced cirrhosis, which signifies that FGF21 analogues are potential pharmacological options for advanced metabolic liver disease[62,63].

4. **Lipogenesis inhibitors:**
Acetyl-CoA carboxylase (ACC) inhibitors like firsocostat and clesacostat are capable to reduce steatosis without changes in body weight or glycaemia; however, those adversely cause an increase in plasma triglyceride levels[64]. Aramchol, a stearoyl CoA desaturase 1 (SCD1) inhibitor demonstrated MASH resolution and fibrosis regression over placebo regarding steatosis improvement in patients with biopsy-confirmed MASH[65].

Combination of drugs:
Combination therapies may increase response rates and effectiveness of treatment, which has so far been limited with monotherapies[66]. A combination of GLP-1RA and SGLT2I in people with type 2 Diabetes, showed additive effects on body weight, glycemic status as well as on MASLD progression[67]. The combination of semaglutide with drugs having weight loss-independent MASH-relieving effects has shown promising results – despite similar weight loss, semaglutide with firsocostat and/or cilofexor are more effective in reducing steatosis compared to semaglutide alone, i.e., 10-11% vs. 8% absolute reduction in liver fat as determined by magnetic resonance imaging (MRI)[68]. Similarly, pairing classical antioxidants like vitamin E with PPARγ agonists might delay MASLD progression by enhancing the scavenging of free radicals and reducing oxidative stress[69].

LIMITATIONS OF THE CLINICAL TRIALS IN MASLD

It is already established that the above described MASLD treatment options have reduced other metabolic comorbidities. However, evidence on their effectively reducing the number of liver-related events, are still not enough[70]. As fibrosis develops slowly over many years and also reverses slowly[71], the main challenge in current clinical trials (mostly having an intervention phase of 12 to 72 months) is failure to adequately detect the changes (in laboratory markers or histologically) or prognosis[72]. This issue has recently been addressed by longer-term follow-up studies – not only in lifestyle modifications but also in drug related treatment interventions. In addition to that MASH resolution correlates with fibrosis regression; however, the assessment of MASH components may be flawed by inter-reader variability[73].

CONCLUSION

Currently, lifestyle modifications aiming at weight loss remain the basis for MASLD treatment due to their favorable effects on metabolic health, although the outcomes may vary from person to person. Metabolic drugs inducing weight loss, especially Incretin mimetics, are valuable tools for achieving MASH resolution but still lack enough evidence of fibrosis regression. Very recently, effective improvement of the different histological MASLD components has been achieved in the clinical trials of drugs which act independently of changes in body weight (e.g., PPAR agonists, FGF21 analogues, lipogenesis inhibitors). Apart from MASH resolution and fibrosis regression, the long-term success of MASLD treatment strategies needs complementary evaluation of endpoints in the future studies.

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