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

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) closely associates with obesity and type 2 Diabetes. Lifestyle interventions, aiming at substantial weight loss, are cornerstones of MASLD, treatment by improving the histological outcomes. Originally developed as antidiabetic drugs, Incretin Mimetics and SGLT2 Inhibitors also reduce steatosis and fibrosis. Certain Incretin agonists effectively improve histological features of MASLD. On the other hand, despite moderate weight gain, one PPARγ agonist was found to improve MASLD with certain benefit on fibrosis in the RCT. We here discuss liver-related outcomes, induced by different MASLD treatment options and their association with weight loss. As such, we have compared results from clinical trials on drugs acting via weight loss (Incretin Mimetics, SGLT2 Inhibitors) with those exerting no weight loss (Pioglitazone). Furthermore, other drugs in development, which directly target hepatic lipid metabolism (lipogenesis inhibitors, FGF21 analogs), have also been addressed.

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Introduction

Recently, based on an international consensus, the term 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, placing a tremendous burden on healthcare sectors [4]. Approximately 10-20 % of people with steatosis progress to "Metabolic dysfunction-associated steatohepatitis" (MASH) [5]. The prevalence of MASH in the general population is projected to rise by 40% within 2030 in Europe [5]. Nowadays, MASLD has evolved as one of the main reasons of liver transplantation in the US and Europe [6,7].

Obesity, Insulin Resistance and MASLD

In people with obesity, MASLD prevalence is estimated to be about 75% [8]. 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]. Consequently, insulin resistance develops, paralleled by altered adipokine (i.e. adiponectin, leptin etc.) secretions and impaired mitochondrial functions, further promoting adipose tissue inflammation [10,11]. Visceral adipose tissue (VAT) compartments also contribute to the

development and progression of MASLD [12]. People with Asian ethnicity show higher VAT accumulation at a given BMI compared to people with Caucasian backgrounds, which may explain the higher prevalence of MASLD in Asian population [21,22]. VAT is associated with higher lipolysis, greater insulin resistance and increased release of pro-inflammatory and pro-fibrogenic mediators [13]. In both obese and lean individuals, VAT mass correlated not only with insulin resistance of liver and adipose tissues but also with liver lipid content and the degree of liver fibrosis [14]. In accordance, the presence of MASLD predicts both the transition from MHO (Metabolically Healthy Obese) to MUO (Metabolically Unhealthy Obese) and future cardiometabolic risk [13,16]. The rate of hepatic de novo lipogenesis is much greater in MASLD, which further contributes to intrahepatic lipid accumulation [15]. 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]. In addition, the presence of hyperglycemia and altered

bile acid secretion patterns also drive MASLD [19,20].

Non-Pharmacological Treatment of MASLD: Lifestyle Interventions

Caloric restrictions can rapidly reduce steatosis and hepatic insulin resistance [22-24]. Histological improvement of different MASLD components depended on the amount of weight loss. Whereas about 5-7 % of weight loss already led to a reduction in liver lipid content in 65 % of people with MASLD, MASH resolution (defined as the absence of hepatocellular ballooning) was achieved in 64 % by a 7-10 % decrease in body weight [25-28]. Reduction in>10% of body weight resulted in a 100 % rate of steatosis improvement, a 90 % rate of MASH resolution and even reversed existing fibrosis by at least one stage in 81 % of people [27]. Healthy dietary habit is also very relevant, as Mediterranean diets showed beneficial effects on liver lipid content [29,30]. These diets rely on plant-based foods. Although 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 likely contributes to lower liver lipid accumulation [31-33]. Other components, such as low intake of red meat and high intake of antioxidant polyphenols, may also mediate the beneficial effects of Mediterranean diets [30,34]. International guidelines {AASLD (American Association for the Study of Liver Diseases), EASL (European Association for the Study of the Liver), ESPEN (European Society for Clinical Nutrition and Metabolism)} also recommend Mediterranean diets for people with MASLD [35-37]. A recent met analysis indicated beneficial effects of gradual weight loss as compared to rapid weight loss in regards to fat mass and basal metabolic rate [38]. 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 of metabolism, which may result in regain of fat mass [39]. Physical exercise improves liver lipid content [40,41]. The combination of diet and exercise are more successful than each intervention alone [42]. As such, current guidelines recommend combating MASLD based on both lifestyle modifications, including a healthy diet and regular exercise [6].

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. Besides weight loss, other drug-elicited effects may contribute in parallel to the recovery of liver homeostasis.

Incretin Mimetics

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) can induce weight loss by central GLP-1 receptor activation in specific regions in the hypothalamus, promoting satiety and decreasing appetite [43,44]. Subsequent reduced caloric intake is regarded as the major mechanism of GLP-1RA-mediated weight loss. The average HbA1c reduction with GLP-1RA in MASLD studies was estimated to be 0.5 % in individuals with and without type 2 Diabetes [45]. Importantly, GLP-1RA reduce the risk of "major adverse cardiac events" (MACE) improve kidney function in people with type 2 diabetes [46]. The primary mediator of the observed improvements in MASH by GLP-1RA treatment is presumably weight loss. Two RCTs with Liraglutide and Semaglutide in mixed collectives of people with and without type 2 diabetes provided evidence for higher rates of histological MASH resolution without worsening of fibrosis compared to placebo. MASH resolution was mainly driven by improvements in steatosis and ballooning for Liraglutide, whereas Semaglutide also reduced inflammation [47,48]. Both treatments were accompanied by a weight loss of 5.5 % and 12.5 % as well as a HbA1c reduction of 0.5 % and 1.2 %, respectively. In people with compensated cirrhosis with and without type 2 diabetes, Semaglutide showed a weight loss of 8.8 % and marked reduction in liver lipid content [49]. Thus, taking into account beneficial 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 [50]. In a small trial in people with biopsy-confirmed MASH without type 2 diabetes, Liraglutide decreased adipose tissue lipolysis as well as leptin levels paralleled by increasing circulating adiponectin [23]. Of note, although Gliptins also inhibit GLP-1-cleaving dipeptidyl peptidase 4 (DPP-4), no clinically relevant effects on liver lipid content, inflammation or fibrosis have been observed with thes group of drugs.

Dual and Triple agonists

RCTs investigating the effects of Tirzepatide (dual agonist) on liver histology in people with MASH are ongoing. After 52 weeks of treatment with the highest dose of Tirzepatide, about 69 % and 43 % of all participants achieved a weight loss of 10% and 15%, respectively, suggesting histologic improvement beyond hepatic steatosis [51,52]. Phase 2 trials investigating the effects of Cotadutide and Survodutide (dual agonists) on histological components of MASH are also ongoing [53]. First results from RCTs with Retatrutide (triple agonist) indicate unprecedented weight loss (24.2% body weight reduction in the obese population) as well as marked reductions in hepatic lipid content, with a subgroup analysis showing MASLD resolution in >85 % of people [54,55].

SGLT Inhibitors

In recent RCTs in cohorts with type 2 diabetes and MASLD, SGLT2I treatment led to a 2-4 % decrease in body weight [56]. Utilizing imaging methods, Canagliflozin failed to induce a statistically significant reduction in liver lipid content, whereas both Dapagliflozin and Empagliflozin were able to reduce liver lipid content in people with type 2 Diabetes, with and without MASLD [56,57]. Of note, the amount of weight loss determined the amount of liver lipid reduction for both Empagliflozin and Canagliflozin in the respective RCTs. In another RCT, Empagliflozin led to a placebo corrected 2.3-fold greater reduction in liver lipid content and a 36 % increase in plasma adiponectin levels in people with type 2 Diabetes [56,58]. In a small-scale pilot study, Empagliflozin reduced steatosis, ballooning and fibrosis after 24 weeks of treatment in people with type 2 Diabetes and MASH when compared to a pretreatment group [59]. A recent 72-week RCT with Ipragliflozin including participants with type 2 diabetes and MASLD, reported higher rates of MASH resolution and fibrosis regression with Ipragliflozin, accompanied by a BMI reduction of 1.06 kg/m2 and decrease in HbA1c of 0.4% [60].

Metformin

Metformin is associated with modest but consistent decrease in body weight (averaging 2% after 1 year) [61,62]. But there is no solid evidence from liver imaging or histology in regards to a beneficial effect of metformin on MASLD components in clinical studies [63,64]. Currently there is only one small scale placebo-controlled study with Metformin. In this study, no differences were detected in histological scores of MASH components and fibrosis between both the groups. Also increased adiponectin levels have

been reported with metformin treatment [65].

Drugs for MASLD Treatment with Weight-Loss-Independent Metabolic Effects

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 [66].

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 [67]. However, pharmacologic targeting of PPARα does not suffice to reduce liver lipid content to a clinically relevant extent [68,69].

PPARγ Agonists

PPARγ is highly expressed in white adipose tissues (WAT) and controls non-esterified fatty acid (NEFA) uptake, lipogenesis as well as reduces adipocyte tissue inflammation [66]. In MASH, treatment with Pioglitazone, the most prescribed PPARγ agonistic drug over the last few decades, was repeatedly associated with improvements in liver histology, despite a net weight gain of 2-4 % of body weight [70,71]. A meta-analysis of 8 RCTs in people with biopsy-proven MASH concluded that Pioglitazone was not only associated with the improvement of MASH, but also reversal of fibrosis [72]. However, the risk-benefit ratio of Pioglitazone remains debatable due to the increased risk of hospitalization from heart failure due to fluid retention [73].

Dual/pan-PPAR Agonists

The dual α/δ PPAR agonist Elafibranor failed to prove superiority to placebo in a 72-week phase 3 study regarding the primary endpoint MASH resolution without worsening of fibrosis (19 vs. 15 % resolution rate) and also for fibrosis improvement (25 vs 22 %) [74]. Lanifibranor, a pan-PPAR agonist, proved effective for MASLD treatment in a 24-week Phase 2b RCT in people with MASH, but displayed similar side effects like Pioglitazone [75].

Modulators of the Mitochondrial Pyruvate Carrier

MSDC-0602 K, a PPARγ-sparing Pioglitazone derivative, was developed to target mitochondrial pyruvate carriers (MPC) 1 and 2 [76-78]. However, a phase 2b RCT in people with biopsy-confirmed MASH and fibrosis failed to meet the predefined histological endpoints [79].

Fibroblast Growth Factor 21 (FGF21) Analogues

Improvements in dyslipidemia and MASLD have been repeatedly observed in clinical trials with FGF21 analogues [80,81]. Recently published results from phase 2 studies with histological endpoints suggested fibrosis regression in people with MASH-induced cirrhosis with Efruxifermin but also Pegozafermin treatment [81,82], which position FGF21 analogues as a potential future pharmacological treatment option for advanced metabolic liver disease.

Lipogenesis Inhibitors

Acetyl-CoA carboxylase (ACC), converts acetyl-CoA to malonyl-CoA and is a rate-limiting step in DNL. During a 12-week RCT in people with MASLD, the ACC inhibitor Firsocostat led to a moderate reduction in steatosis without changes in body weight or glycemia, but adversely caused an increase in plasma triglyceride levels [83]. Another ACC inhibitor, Clesacostat, showed an even more pronounced reduction of liver lipid content in a 16-week RCT but also led to greater increases in plasma triglyceride levels [84]. Aramchol, an inhibitor of stearoyl coenzyme A desaturase 1 (rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids), demonstrated only a numerical benefit over placebo regarding steatosis improvement in a 52-week phase 2 RCT in people with biopsy- confirmed MASH [85]. In contrast, for MASH resolution and fibrosis regression, the drug was superior to placebo.

Combination of Drugs

On one hand, drug combinations may increase response rates and effectiveness of treatment, which has so far been limited with monotherapies [86]. A RCT on the 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 [87]. The combination of Semaglutide with drugs having weight loss-independent MASH-relieving effects is currently tested in a trial [88]. Semaglutide and Firsocostat or Cilofexor were more effective in reducing steatosis compared to semaglutide alone (8 vs. 10-11 % absolute reduction in liver fat determined by magnetic resonance imaging) despite similar weight loss [88].

Limitations of the Clinical Trials

It is already established that the above described MASLD treatment options have reduced other metabolic comorbidities. But evidence on their effectively reducing the number of liver-related events, are still not enough [89]. As fibrosis develops slowly over many years and also reverses slowly [90], this bears the risk that current clinical trials, with most of them including an intervention phase of 12 to 72 months, may not adequately detect the changes in prognosis [91]. This issue has recently been addressed by longer-term follow-up studies, not only for lifestyle interventions but also for drug treatments. Although MASH resolution correlates with fibrosis regression, assessment of MASH components may be flawed by inter-reader variability [92].

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 (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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