Editorial Commentary

Resmetirom as an important cornerstone of multidisciplinary management of metabolic dysfunction-associated steatohepatitis

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease worldwide, which can develop into metabolic dysfunction-associated steatohepatitis (MASH), associated with steatosis, liver cell damage, inflammation, and fibrosis. Diagnostic methods, lifestyle interventions, medications, and surgical treatments of MASLD/MASH have been studied in the medical community and capital markets. Resmetirom was the first drug conditionally approved by the Food and Drug Administration (FDA) for the treatment of MASH on 14 March, 2024, currently leading the pharmaceutical treatment field. The study of effectiveness, safety, differentiation, and cost-effectiveness of the use of resmetirom needs to be continued. The concept of MASH for simultaneous multidisciplinary management should be studied and promoted, including non-invasive diagnosis, lifestyle interventions, pharmacotherapy, and metabolic and bariatric surgery (MBS). Through efforts from those directions, the treatment of MASH was promoted.

The first phase 3 trial of resmetirom was entitled MAESTRO-NAFLD-1, which was a 52-week randomized, double-blind, placebo-controlled trial evaluating the safety of resmetirom in adults with MASLD and presumed MASH (1). The study was published on *Nature Medicine* entitled "Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial" by Harrison *et al.* in 2023. This trial found a decrease in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), triglycerides (TGs), liver fat, liver hardness, and liver fat in subjects including 80- and 100-mg of resmetirom, in comparison with placebo. Findings suggested that resmetirom is safe and well tolerated in adult patients presumed to MASH but needs to beware of adverse effects, including diarrhea and nausea. This led to another phase 3 clinical trial with greater clinical significance, which in turn led to FDA approval, bringing new hope to the treatment of MASH and resolving the dilemma of MASH patients having no available medicine.

Nutrition and lifestyle for patients with MASH

The impact of MASLD/MASH is growing in the context of the obesity epidemic. High liver fat content increases the risk of hepatic and extra-hepatic progression in MASLD, and liver fat reduction is required (2). Lifestyle interventions focused on healthy nutrition and appropriate physical activity are the cornerstones of treatment. Physical exercise alone or in combination with dietary intervention can improve liver serology and histology, and exercise is beneficial in reducing liver TGs even in the absence of weight loss (3). Controlling patient's dietary pattern is important to prevent the progression of liver pathology, we recommend personalized lifestyle interventions using

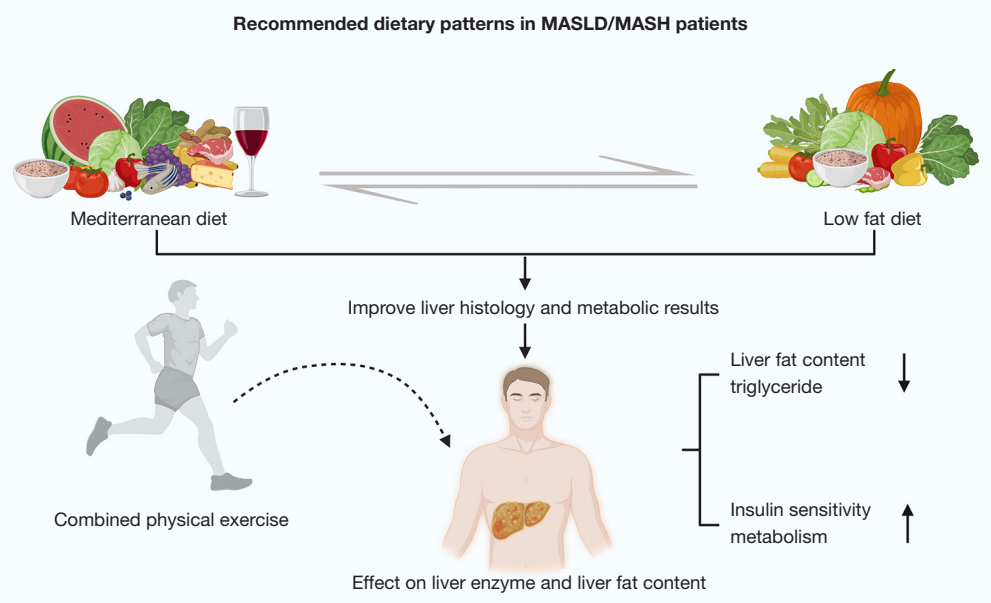

Figure 1 Recommended dietary patterns in MASLD/MASH patients. The MD and LFD is suggested to use in combination with physical exercise for personalized lifestyle intervention, which can significantly improve visceral fat, and have similar therapeutic effects on liver enzymes and liver fat content. Created in BioRender. Au K. [2024]. BioRender.com/g95h140. ↑, increase; ↓, decrease. LFD, low-fat diet; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MD, Mediterranean diet.

a Mediterranean diet (MD) and low-fat diet (LFD), at the same time with personalized exercise physical activity. A randomized controlled trial (RCT) noted that there were no statistical differences in liver and metabolism between MD and LFD, visceral fat was significantly improved (4). MD and LFD have similar therapeutic effects on liver enzymes and liver fat content in MASLD patients in the short term, new avenues can be opened up in the concept of interchanging MD and LFD (5). These diet patterns reduce liver fat content and TGs, improve insulin sensitivity and liver metabolism (*Figure 1*). Also, excessive accumulation of TGs in the body and liver can also lead to MASLD. Meanwhile, beverages containing high fructose corn syrup have been linked to metabolic abnormalities and have led to the development of MASLD in human trials, need attention to eating patterns and balance (6). While the role of dietary intervention existed, it is currently challenging to provide dietary intervention to adult MASLD/MASH patients due to time/financial cost or personal reasons. More rigorous RCT and clinical study are needed to provide robust quantitative evidence of the impact of these dietary patterns, as well as other approaches, on MASLD/MASH progression.

MBS for patients with MASH

Due to pathophysiological properties, MASLD and MASH are common in patients with obesity which can be improved after MBS. With the increase of MASLD, the role of MBS in the realization of liver compensation has received increasing attention. However, the complexity of preoperative evaluation, the risk of postoperative recurrence, and the possibility of complications of MBS pose challenges (7). MBS has great potential and effectiveness in the treatment of MASH. MBS determined long-term weight loss and had a positive effect on MASH resolution without fibrotic progression (8). Regression of MASH in liver samples was observed in 84% of patients after 5 years by MBS, and the reduction in fibrosis was progressive (9). In an RCT, the efficacy of MBS for MASH was compared with the efficacy of lifestyle interventions and medication, MBS was found to be more effective than lifestyle interventions and medication in treating MASH (10). There is widespread discussion about which surgical approach to use for MBS in obesity and MASH, and studies on safety and efficacy are also ongoing, with sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) being the most widely used (*Figure 2*).

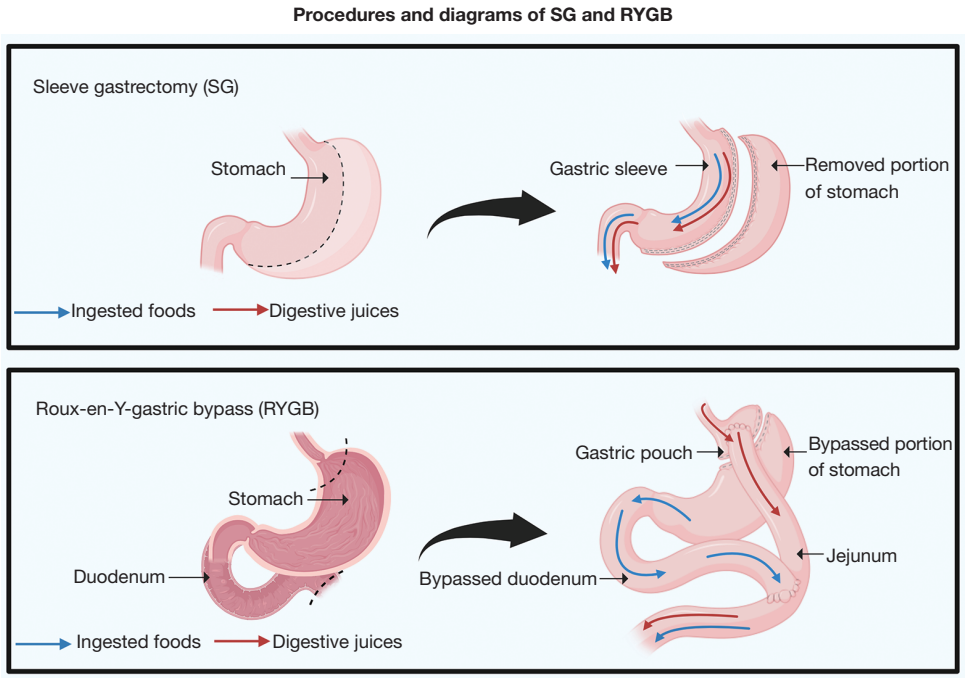

Figure 2 Procedures and diagrams of SG and RYGB. The SG and RYGB is mainly suggested to use in MBS for obesity and diabetes, efficacy and safety MBS in patients with MASH has also been progressively proven. Created in BioRender. Au K. [2024]. BioRender.com/c49i939. MASH, metabolic dysfunction-associated steatohepatitis; MBS, metabolic and bariatric surgery; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

MASH can significantly improve the histological features of patients with obesity, which is an alternative treatment option for patients who have failed to respond to lifestyle intervention or medication (11). There is also an unmet clinical need for reliable non-invasive diagnostic tools, in morbidly patients with obesity undergoing MBS, magnetic resonance imaging (MRI) was superior to controlled attenuation parameter (CAP) in diagnosing MASLD, grading steatosis, and excluding severe MASH (12). There is currently a lack of quantitative data on which surgical approach to choose, and more research is needed on the effects of surgical approaches on the treatment of MASH.

Multidisciplinary management of MASH with resmetirom

A multidisciplinary management is important for MASLD/MASH patients. In our recent research, we proposed specific implementation methods of multidisciplinary management of MASH (13). Along with the recent approval of resmetirom, a promising multidisciplinary management program was mentioned. In this phase 3 trial, approximately one-third of the randomized patients underwent baseline liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), demonstrating the effectiveness and feasibility of non-invasive diagnostic tools (1). Definitive diagnosis of MASH currently relies on invasive and labor-intensive liver biopsies. In a recent study, soluble CUB domain protein 1 (sCDCP1) was found to be the preferred non-invasive biomarker for MASH in individuals with obesity with liver biopsies (14). Therefore, a non-invasive SCDCP1-based test could potentially be used to screen for and early diagnose MASH to avoid unnecessary liver biopsies. Combining of non-invasive diagnostic methods, lifestyle interventions, effective medication, and MBS to achieve a reliable multidisciplinary management. As for the selection of drugs, resmetirom should be placed in the existing drug background for clinical comparison in the future, examples include vitamin E, metformin, semaglutide, and others that are currently in clinical trials. The same is true for the selection of surgical methods, examples included SG and RYGB which need to be quantitatively compared with various methods. A multidisciplinary management have a

good impact on MASH, combining the strengths of each discipline. Quantitative data on the safety and effectiveness of multidisciplinary management needs to be supplemented.

Challenges and limitations of MASH with resmetirom

In phase 3 clinical trials in 2023, resmetirom was well tolerated at both 80- and 100-mg once daily doses over 52 weeks of treatment. However, excessive treatment emergent adverse event (TEAE) appeared to be mainly gastrointestinal (diarrhea and nausea) and were moderate at the beginning of treatment with resmetirom, but very few patients discontinued the study because of TEAE, women had a higher incidence of nausea compared with placebo (1). The phase 3 trial in 2024 also redemonstrated that 80- and 100-mg doses of resmetirom were superior to placebo in at least one phase of MASH remission and liver fibrosis improvement. However, the incidence of diarrhea and nausea was higher than that of the placebo group. The incidence of serious adverse events was similar across the trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group and 11.5% in the placebo group (15). Solutions need to be developed in future studies to prevent patients from abandoning it due to adverse reactions. Also, the current price of resmetirom is relatively expensive, which is not conducive to social promotion, and the use of resmetirom in low-income countries has great economic problems. Research and policy support will be needed to promote universality in the future.

Conclusions

The FDA's conditional approval is a milestone in the treatment of MASH and provides a much-needed pharmaceutical intervention, also under review in the European Union. If approved locally, adults with MASH and liver fibrosis could be added to a targeted therapy with resmetirom. Due to the complexity of MASH, a multidisciplinary approach to treatment is needed, we advocate multidisciplinary treatment such as non-invasive diagnostic methods, lifestyle interventions, effective medication, and MBS. It is important to properly reduce the price, so as to achieve true universality and help patients with MASH in need, promotion in society is important.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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