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Metabolic Dysfunction-Associated Steatotic Liver Disease: Progress, Challenges, and Prospects of Precision Medicine

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed nonalcoholic fatty liver disease (NAFLD), has emerged as one of the most prevalent chronic liver diseases globally, affecting nearly 30% of the adult population, with rising incidence rates across all age groups, including younger individuals [1, 2]. This disease is closely linked to the increasing burden of obesity, type 2 diabetes, and metabolic syndrome, reflecting a global shift towards sedentary lifestyles and unhealthy dietary habits. The renaming of NAFLD to MASLD underscores its strong association with systemic metabolic dysfunction, which drives disease progression and highlights its multifaceted nature [3]. Importantly, MASLD is not only a leading cause of end-stage liver complications, such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), but also contributes to significant extrahepatic burdens, including cardiovascular disease, chronic kidney disease, and diabetes-related complications [4].

The management of MASLD presents unique challenges due to its heterogeneity in disease progression, which is influenced by genetic predisposition, age, sex, ethnicity, and environmental factors [5]. Current diagnostic tools, such as imaging techniques and hematological scoring systems, have limited sensitivity for detecting early disease stages or mild fibrosis [6]. Similarly, therapeutic options remain constrained, with lifestyle modifications representing the mainstay of intervention and only a few emerging pharmacological agents showing promise in clinical trials [7]. This highlights an urgent need for innovative approaches to diagnose better, stratify, and manage MASLD in a personalized manner.

Precision medicine, an emerging paradigm in healthcare, offers transformative potential for addressing these challenges. By integrating individual genomic, proteomic, and metabolomic data with clinical and environmental factors, precision medicine enables the identification of novel biomarkers, accurate disease classification, and tailored therapeutic strategies [8]. This approach is particularly suited to MASLD, given its diverse clinical manifestations and complex pathophysiology. Recent advancements in multi-omics technologies and data-driven analytics have paved the way for comprehensive phenotyping of MASLD, revealing molecular subtypes with distinct prognostic and therapeutic implications. Furthermore, the advent of predictive models and targeted therapies offers hope for earlier interventions and improved clinical outcomes.

In this review, we explore the current progress and future directions of precision medicine in MASLD, focusing on its application in diagnosis, treatment, and long-term disease management. By addressing the limitations of traditional approaches and emphasizing the potential of precision strategies, this article aims to provide a comprehensive framework for advancing MASLD research and clinical practice.

Accurate Diagnosis: From Single Diagnostic Biomarkers to Comprehensive Indicators

Accurate diagnosis of MASLD is complicated by its heterogeneous clinical manifestations and the lack of highly sensitive and specific diagnostic tools. Conventional diagnostic methods, including imaging techniques like FibroScan and MRI-PDFF, and hematological scoring systems such as FIB-4 and NAFLD fibrosis scores, are widely used due to their non-invasive nature and clinical accessibility [9]. However, these tools demonstrate limited sensitivity and specificity in detecting early-stage disease or mild fibrosis, particularly in patients with obesity or inflammatory comorbidities. For instance, FIB-4 scores often fail to differentiate intermediate fibrosis stages, while MRI-PDFF, despite its high specificity, is costly and not widely available, limiting its applicability in routine clinical practice [10]、[11]. These limitations emphasize the need for more precise and accessible diagnostic methods.

Application of Multi-Omics Studies

Recent advancements in multi-omics technologies have revolutionized MASLD diagnostics by uncovering molecular mechanisms and identifying novel biomarkers. Genomic studies have revealed several key genetic variants, such as PNPLA3, TM6SF2, MBOAT7, and HSD17B13, significantly influencing MASLD susceptibility and progression [12]. Among these, the PNPLA3 I148M polymorphism has emerged as a critical biomarker, closely associated with hepatic steatosis, fibrosis, and HCC [13]. This mutation enhances lipid accumulation within hepatocytes, activates hepatic stellate cells, and contributes to fibrotic tissue formation, making it a valuable target for risk stratification [14]. Furthermore, population-specific studies have highlighted the varying prevalence and impact of these mutations across different ethnicities, underscoring the importance of tailoring diagnostic approaches to diverse populations.

Epigenetic modifications, including DNA methylation and histone modifications, have also been implicated in MASLD pathogenesis. For example, CpG sites associated with liver fibrosis identified using 850K methylation arrays hold potential as novel diagnostic and prognostic tools. Despite these promising findings, the clinical implementation of such biomarkers remains limited due to the need for large-scale validation studies and cost-effective testing methods [15]. In proteomics and metabolomics, significant strides have been made in identifying non-invasive biomarkers. Proteomic analysis of serum, urine, and liver tissue samples from MASLD patients has uncovered differentially expressed proteins involved in pathways such as cell adhesion, immune response, and carbohydrate metabolism. These biomarkers enable the stratification of patients based on the severity of inflammation and fibrosis [16]. Similarly, metabolomic profiling has revealed distinct lipid signatures and metabolic pathways associated with MASLD subtypes, offering insights into disease mechanisms and potential therapeutic targets. However, further research is needed to validate these findings and translate them into clinical practice.

Integrated Multi-Omics Approaches in Subtype Diagnosis

The integration of multi-omics data has facilitated a deeper understanding of MASLD heterogeneity and provided the basis for novel disease classification systems. For instance, multi-omics

analyses combining genomic, proteomic, lipidomic, and metabolomic data have identified three clinically relevant MASLD subtypes: metabolically active type, high-risk cirrhotic type, and high-risk HCC type [17]. Each subtype is characterized by distinct biomolecular signatures, enabling more precise risk stratification and targeted therapeutic strategies. Such integrative approaches offer a comprehensive view of MASLD pathophysiology, bridging the gap between molecular insights and clinical applications.

Innovative methodologies, such as partitioned polygenic risk scores (pPRS), have further refined MASLD subtyping [18]. By evaluating genetic risk factors across multiple pathways, pPRS distinguishes a liver-specific subtype associated with advanced liver disease from a systemic subtype linked to cardiovascular risk. While promising, these approaches face challenges related to scalability, cross-population validation, and the integration of clinical and genetic data.

In a complementary effort, the Hubei Institute of Traditional Chinese Medicine Liver Diseases has applied a data-driven framework incorporating protein-protein interaction networks, drug target information, and Traditional Chinese Medicine phenotypes to classify MASLD patients into five distinct subgroups [19]. These include patients with chronic liver disease and decompensated complications, those with digestive system disorders, individuals with type 2 diabetes and its complications, patients with immune system diseases and mental health issues, and women with gynecological conditions. Such frameworks highlight the potential of integrating multi-omics data with clinical records to achieve personalized MASLD management.

Challenges and Future Directions

Despite the transformative potential of multi-omics diagnostics, their clinical adoption is hampered by several challenges. High costs, technical complexity, and the lack of standardized protocols remain significant barriers. Furthermore, most multi-omics studies to date have been conducted on small, homogeneous cohorts, limiting their generalizability to diverse patient populations. Future efforts should focus on large-scale, multicenter validation studies, the development of cost-effective testing platforms, and the integration of omics data with digital health technologies. By addressing these challenges, multi-omics approaches have the potential to revolutionize MASLD diagnostics, enabling earlier detection, accurate risk stratification, and personalized therapeutic strategies.

Precision Therapy: From Lifestyle Interventions to Novel Drugs and Combination Therapies

The treatment strategies for MASLD are evolving rapidly, encompassing foundational lifestyle interventions, innovative drug therapies, and the potential of combination treatments tailored to individual disease subtypes. These approaches highlight the complexity of MASLD pathogenesis and the critical need for precision in clinical management.

Lifestyle Interventions: The Cornerstone of MASLD Management

Lifestyle modifications remain the cornerstone of MASLD management, with robust evidence supporting their effectiveness in improving hepatic steatosis and inflammation. Weight loss through dietary adjustments and increased physical activity has been shown to yield significant benefits, with reductions of 5%-10% in body weight associated with marked improvements in liver health. Notably, weight loss of ≥10% can potentially reverse fibrosis, underscoring the importance of sustained behavioral changes [20]. Long-term adherence, however, remains a challenge, and meta-analyses have highlighted the variable success rates of lifestyle interventions in different populations. Recent clinical guidelines emphasize the integration of multidisciplinary support, such as dietary counseling and structured exercise programs, to enhance adherence and optimize outcomes. Digital health technologies, including mobile apps and wearable devices, also show promise in supporting sustained lifestyle changes [21].

Advances in Novel Drug Development

The emergence of novel pharmacological agents offers new hope for MASLD patients, particularly those who are unable to achieve sufficient results through lifestyle modifications alone.

Thyroid Hormone Receptor-β Agonists: Resmetirom, recently approved by the FDA, represents a milestone as the first drug specifically targeting MASLD. By modulating thyroid hormone pathways, Resmetirom has demonstrated significant reductions in liver fat content and fibrosis in clinical trials, with a favorable safety profile compared to existing treatments [22].

Glucagon-like peptide-1(GLP-1) Receptor Agonists: Semaglutide, a GLP-1 receptor agonist, has gained attention for its dual benefits in weight management and glycemic control. Phase III trials reveal that Semaglutide not only facilitates significant weight loss but also improves liver fibrosis and inflammation, outperforming standard therapies in certain patient subgroups [23].

Fibroblast Growth Factor 21 (FGF21) Analogs: Eflomosfermin, an FGF21 analog, has shown notable efficacy in reducing liver fibrosis and inflammation. Its low-frequency dosing regimen (once-monthly injection) enhances patient compliance, a critical factor in long-term MASLD management. However, larger-scale trials are needed to establish its comparative effectiveness against other emerging therapies [24].

Nucleic Acid-Based Therapies: Innovations in nucleic acid-based treatments, such as small interfering RNA (siRNA) and antisense oligonucleotides (ASO), provide a targeted approach by modulating key genetic drivers of MASLD. For example, siRNA therapies targeting PNPLA3 and HSD17B13 have shown potential in reducing liver fat accumulation and fibrosis. However, these therapies face challenges in delivery mechanisms, cost, and long-term safety, necessitating further research to facilitate clinical translation [25].

The Future of MASLD Therapy: Combination Treatments and Personalization

While monotherapies have demonstrated promising results, combination therapies targeting multiple pathological pathways are likely to represent the future of MASLD treatment. For example, combining GLP-1 receptor agonists with anti-fibrotic agents such as FGF21 analogs may provide synergistic benefits by addressing both metabolic dysfunction and fibrosis [26]. Preliminary studies suggest that such combinations could enhance therapeutic efficacy while minimizing side effects, although robust data from large-scale clinical trials are still lacking.

Additionally, personalized treatment approaches tailored to specific MASLD subtypes offer significant promise. Multi-omics research has paved the way for stratifying patients into subtypes based on genetic, proteomic, and metabolic profiles, enabling more precise therapeutic targeting. For example, patients with the liver-specific subtype characterized by advanced fibrosis may benefit more from anti-fibrotic agents, while those with systemic metabolic dysfunction may require therapies targeting cardiovascular risk factors [1]. Incorporating predictive models and artificial intelligence into clinical decision-making could further refine treatment strategies, optimizing outcomes for individual patients.

Challenges and Opportunities in MASLD Therapeutics

Despite these advancements, several challenges remain. The high costs associated with novel drugs and multi-omics-based diagnostics pose significant barriers to widespread adoption [27]. Moreover, the lack of long-term data on the efficacy and safety of emerging therapies necessitates further clinical validation. Collaborative efforts between researchers, clinicians, and industry stakeholders are essential to address these challenges and advance MASLD therapeutics. Furthermore, improving patient access to innovative treatments through policy changes and cost reductions will be critical to ensuring equitable care.

Prospects of Precision Medicine: From Diagnosis to Management

Integration of Multi-Omics and Predictive Models

The integration of multi-omics data, including genetics, proteomics, metabolomics, and clinical information, provides a foundation for developing precise predictive models for MASLD progression. These models enable early identification of high-risk patients and timely interventions. For example, researchers at Guangdong Provincial People's Hospital analyzed plasma proteomics data from over 50,000 participants without MASLD, incorporating clinical data to identify key proteins linked to disease onset. Using multivariate Cox regression analysis, they developed a predictive model capable of detecting MASLD risk up to 16 years prior to disease onset, achieving an AUC (Area Under the Curve) of 0.90 [28]. This model represents a significant advancement over current tools, providing a transformative platform for early screening and precision interventions. However, the clinical application of such predictive models faces challenges, including the standardization of data integration protocols, validation in diverse populations, and accessibility in routine clinical settings. Future efforts should focus on incorporating machine learning algorithms to refine predictive accuracy and integrate additional clinical variables, such as imaging and metabolic profiles. These advancements could enable more personalized treatment recommendations and better disease management strategies.

Development of Novel Drugs and Combination Therapies

The continuous evolution of pharmacological strategies for MASLD highlights the potential of novel drugs and combination therapies. Lanifibranor, a PPAR pan-agonist, has demonstrated efficacy in modulating nuclear receptor pathways, regulating multiple gene expressions, and addressing various MASLD-related pathophysiological processes [29]. This drug represents a promising direction for comprehensive MASLD treatment. Professor Cui Yimin's team developed an innovative drug, HSK31679, which not only targets hepatic thyroid hormone receptor-β but also inhibits gut-derived sphingolipid glycosylation [30]. This dual mechanism selectively recruits bone marrow-derived cells with immunosuppressive properties, offering a novel approach to slowing MASLD progression. Such combination therapies targeting distinct pathological pathways can enhance treatment efficacy while minimizing side effects. Despite these promising developments, combination therapies face challenges, including high costs, limited large-scale clinical trial data, and the complexity of optimizing dosages and schedules. Collaborative efforts to standardize treatment protocols and conduct multicenter trials are crucial to advancing these therapies into routine practice.

Digital Health Management

Digital health technologies, including the Internet of Things, artificial intelligence, and big data, offer unprecedented opportunities to enhance MASLD management. These technologies enable real-time collection and analysis of patient health information, facilitating long-term lifestyle interventions and dynamic evaluation of treatment efficacy. For example, digital intervention tools developed using intervention mapping have successfully supported MASLD patients in initiating and sustaining dietary and exercise changes, contributing to significant weight loss and improved liver outcomes [31]. Additionally, mobile health applications designed for lifestyle guidance have demonstrated improvements in both physical and psychological health among MASLD patients. Wearable devices, remote monitoring systems, and AI-driven personalized feedback systems further enhance patient adherence and outcomes [32]. While digital health technologies hold immense potential, their widespread adoption faces barriers such as cost, data privacy concerns, and the need for robust validation studies. Ensuring equitable access and integrating these technologies into existing healthcare systems will be critical for their success in MASLD management.

Challenges and Future Directions

Precision medicine is poised to revolutionize the management of MASLD. By integrating predictive models, innovative drugs, and digital health technologies, it offers unprecedented opportunities for early diagnosis, targeted treatment, and personalized care. However, the transition from theoretical frameworks to clinical implementation faces significant barriers. Data standardization and integration remain critical challenges, as the lack of uniform protocols for multi-omics analysis limits the comparability and scalability of findings. Economic constraints also pose a major hurdle, with the high costs of diagnostics and therapies restricting access for many patients. In addition, ethical concerns related to data privacy and informed consent must be addressed to build trust and ensure equitable application of these advancements.

Despite these challenges, the future of MASLD management is promising. Continued progress in multi-omics technologies, coupled with large-scale clinical trials, will likely accelerate the translation of precision medicine into practice. Interdisciplinary collaboration among hepatologists, geneticists, data scientists, and policymakers will be essential to overcome existing obstacles and optimize research and healthcare delivery. By fostering international cooperation and prioritizing patient-centered care, precision medicine holds the potential to provide MASLD patients with more effective, accessible, and sustainable treatment solutions.

Conclusion

Precision medicine is poised to revolutionize the management of MASLD. From the development of predictive models and innovative drugs to the integration of digital health technologies, precision medicine offers unparalleled opportunities for early diagnosis, targeted treatment, and personalized care. However, significant barriers remain, including data standardization, economic constraints, and ethical considerations.

With continued advancements in multi-omics technologies and the implementation of large-scale clinical trials, precision medicine is expected to move from theoretical frameworks to widespread clinical practice. Collaborative efforts across disciplines and international boundaries will be critical to ensuring that precision medicine delivers its full potential, providing MASLD patients with more effective, accessible, and sustainable treatment solutions.

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Competing interests

The authors declare no conflicts of interest.

Abbreviations

MASLD, Metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; GLP-1, glucagon-like peptide-1; FGF21, Fibroblast Growth Factor 21.

Citation

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