MASH: Why diabetes management now demands a liver-first approach?

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Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), represents a growing public health challenge, particularly given its strong association with type 2 diabetes and metabolic syndrome. For years, management has focused on lifestyle interventions and addressing comorbidities, but direct pharmacological interventions for MASH itself have been elusive.
But a new wave of liver-directed therapies is beginning to offer more targeted approaches, moving beyond systemic metabolic control to directly impact hepatic inflammation and fibrosis. These developments demand a closer look from diabetes specialists, as they will increasingly encounter patients eligible for these novel treatments.

KEY TAKEAWAYS

- The Pivot: Liver-directed therapies are moving beyond systemic metabolic control to directly target hepatic inflammation and fibrosis in MASH.
- The Data: Specific numeric results are not available for this general content.
- The Action: Diabetes specialists should understand these emerging MASH treatments, as they will need to identify appropriate patients and collaborate on management strategies.

MASH is characterized by hepatic steatosis, inflammation, and hepatocellular ballooning, often progressing to fibrosis and cirrhosis. This progression carries a substantial risk of liver-related morbidity and mortality, including hepatocellular carcinoma and the need for liver transplantation. The disease is intimately linked with insulin resistance, obesity, and dyslipidemia, making it a common comorbidity in patients managed by diabetes specialists. Current guidelines emphasize weight loss, dietary changes, and exercise as foundational, but these interventions often fall short in halting disease progression, especially in those with advanced fibrosis.
The unmet need for effective pharmacological therapies in MASH has driven extensive research into agents that can directly modify the disease process within the liver. This includes compounds targeting specific pathways involved in lipid metabolism, inflammation, and fibrogenesis. The goal is not merely to improve metabolic parameters, but to achieve histological improvement, defined as a reduction in MASH activity score and/or regression of fibrosis without worsening MASH.

The Rationale for Liver-Directed Approaches

The liver is the central organ in MASH pathogenesis, making it a logical target for therapeutic intervention. Systemic therapies, while beneficial for associated metabolic conditions, often have indirect or insufficient effects on the specific

inflammatory and fibrotic pathways within the liver. Liver-directed agents aim to achieve higher concentrations at the site of disease, potentially leading to more potent and specific effects on hepatocytes, Kupffer cells, and hepatic stellate cells.

These agents often work by modulating nuclear receptors, such as farnesoid X receptor (FXR) agonists, or by inhibiting specific enzymes involved in lipid synthesis or inflammatory cascades. For instance, FXR activation plays a critical role in regulating bile acid synthesis, glucose homeostasis, and lipid metabolism, offering a multi-pronged attack on MASH pathology. Other approaches include thyroid hormone receptor beta (THR-β) agonists, which primarily act on the liver to promote fatty acid oxidation and reduce hepatic steatosis, or inhibitors of acetyl-CoA carboxylase (ACC), which reduce de novo lipogenesis.

The specificity of these agents to hepatic pathways is a key advantage. By concentrating their action in the liver, they may offer a more favorable safety profile compared to systemic agents that could impact multiple organ systems. This precision is particularly important in a patient population often burdened with multiple comorbidities and polypharmacy. Understanding these mechanisms is essential for diabetes specialists, as many of their patients will be candidates for these therapies, and the relationship between these agents and existing diabetes medications will need careful consideration, as discussed in our previous coverage on unraveling MASH.

But the challenge remains in identifying the right patient for the right therapy. MASH is a heterogeneous disease, and not all patients will respond equally to a single mechanism of action. The development of non-invasive diagnostic markers for MASH and fibrosis staging is therefore essential to guide treatment decisions, as highlighted by discussions around MASH diagnosis at recent conferences.

Impact on Diabetes Management

For diabetes specialists, the advent of liver-directed MASH therapies introduces a new dimension to patient care. Many patients with type 2 diabetes have concomitant MASH, often undiagnosed or underestimated in its severity. The presence of MASH significantly increases the risk of cardiovascular events and chronic kidney disease, beyond the risks posed by diabetes alone. Effective MASH treatment could therefore have broader benefits for overall metabolic health and long-term outcomes.

The integration of these new therapies into existing diabetes management protocols will require careful coordination. Diabetes specialists are uniquely positioned to identify patients at risk for MASH, given their expertise in metabolic disorders. Screening for MASH in diabetic populations, particularly those with elevated liver enzymes or imaging evidence of steatosis, becomes even more imperative. The Oxford Handbook of Endocrinology and Diabetes provides a practical reference for managing these complex interconnections.

But the question of how these liver-directed agents will interact with established diabetes medications, such as GLP-1 receptor agonists or SGLT2 inhibitors, is still being explored. While some diabetes medications have shown incidental benefits on liver fat, the new MASH-specific drugs are designed for direct histological improvement. Clinicians will need to navigate polypharmacy, potential drug-drug interactions, and the cumulative impact on patient safety and tolerability. This requires a holistic view of the patient's metabolic profile and liver health.

The long-term efficacy and safety data for these liver-directed therapies are still maturing. While early results may show histological improvements, the ultimate impact on hard clinical endpoints like progression to cirrhosis, liver failure, or hepatocellular carcinoma will take years to fully elucidate. This means that while the enthusiasm for these new agents

is warranted, a pragmatic approach to their adoption is essential, focusing on patients with clear evidence of progressive disease and advanced fibrosis.

The Path Forward for Clinical Practice

The evolving treatment landscape of MASH necessitates a multidisciplinary approach. Diabetes specialists will need to collaborate closely with hepatologists to ensure appropriate patient selection, monitoring, and management. This includes understanding the nuances of liver biopsy interpretation, non-invasive fibrosis assessment, and the specific indications and contraindications for each liver-directed agent. The goal is to optimize patient outcomes by addressing both their diabetes and their liver disease in a coordinated manner.

Education on MASH and its management will be vital for diabetes specialists to ensure appropriate patient care. This goes beyond understanding the mechanisms of action of new drugs; it involves recognizing the signs of advanced liver disease, interpreting liver function tests in the context of MASH, and knowing when to refer to a hepatologist. The complexity of MASH, and why our old view of steatosis, inflammation, and fibrosis often fails, is a topic we have explored previously in our insights section.

The open-label design of some early studies is an obvious caveat, and the reliance on surrogate endpoints like histological improvement, while necessary for early development, means that real-world clinical benefit still needs to be definitively established. The patient population in many trials often excludes those with decompensated cirrhosis or other severe comorbidities, meaning the benefits may not extend to the sickest patients seen in routine practice. This gap matters for clinical decision-making.

The next generation of trials will need to focus on longer-term outcomes, head-to-head comparisons with existing or emerging therapies, and the impact on diverse patient populations. Only then will the full clinical utility of these liver-directed approaches become clear, allowing for their confident integration into standard care for patients with moderate to advanced MASH.

> **CLINICAL IMPLICATIONS**
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> The shift towards liver-directed therapies for MASH fundamentally alters the clinical landscape for diabetes specialists. No longer can MASH be viewed solely as a secondary consequence of metabolic dysfunction; it demands direct intervention. Clinicians must now actively screen for and stage MASH in their diabetic patients, particularly those with elevated liver enzymes or imaging findings, to identify candidates for these emerging treatments.
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> But the integration will not be seamless. The sheer number of new agents, each with distinct mechanisms and safety profiles, will require a steep learning curve. Diabetes specialists will need to understand the specific histological endpoints and the nuances of fibrosis regression, moving beyond general improvements in metabolic markers. This necessitates a closer working relationship with hepatology colleagues, ensuring a truly multidisciplinary approach to patient care.
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> For the pharmaceutical industry, the focus on liver-directed MASH therapies represents a significant commercial opportunity, but also a challenge in demonstrating clear, long-term clinical benefit over and above existing metabolic interventions. The market will demand robust evidence of reduced liver-related events, not just histological changes. Patients, in turn, will face complex treatment decisions, balancing potential benefits

against the risks of novel agents and the burden of polypharmacy.

The unanswered question remains whether these liver-directed therapies will ultimately translate into a reduction in hard clinical outcomes like liver transplantation or liver cancer. While histological improvement is a positive step, the true measure of success will be preventing the devastating consequences of advanced liver disease.

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