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Metabolic Pharmacotherapy for NAFLD/NASH: A Collaborative Approach to Finding New Treatments

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Key Focus Points

- Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are highly prevalent multi-system disorders that represent major threats to public health.
- Improved knowledge of the metabolic etio-pathophysiology of NAFLD/NASH has stimulated intense efforts to develop safe and effective pharmacological interventions. Many of the drugs that have been evaluated as potential treatments for NAFLD/NASH or are currently in development are classified as having metabolic or cardiometabolic actions
- We propose a collaborative approach to the development of new pharmacotherapies for NAFLD/NASH that brings together expertise in clinical hepatology, diabetes and human metabolism

Background

Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most common liver disease globally with population-based estimates of approximately 20-30%. Men are more likely to be affected than women. Ethnicity modifies the prevalence of NAFLD with Hispanics being disproportionately affected relative to whites and blacks. Among patients with type 2 diabetes the prevalence of NAFLD approaches 70% rising to 90% in the presence of morbid obesity.

NAFLD embraces a wide range of metabolic hepatic damage characterized by steatosis that carries a risk of progression to NASH (non-alcoholic steatohepatitis) in a proportion of affected individuals. NASH is characterized by liver cell injury and inflammation in addition to excessive fat deposition. While fibrosis is not part of the definition of NASH the presence of fibrosis is an important prognostic marker (see below).

The diagnosis of NAFLD, which remains largely subclinical during the early stages of development, is problematic. This difficulty reflects the low sensitivity and specificity of imaging and standard clinical chemistry assessments of hepatic function. These considerations are also relevant to the design of clinical trials assessing the efficacy of novel treatments. NAFLD is defined as the presence of >5% hepatic fat content in the absence of other recognized in the absence of other causes of fatty liver, e.g., alcohol, viruses, certain drugs, autoimmune disease. In clinical practice, a diagnosis of NAFLD is established by abnormal liver chemistry, imaging studies (usually starting with ultrasound as the first step) with liver biopsy being reserved for selected cases at high risk of non-alcoholic steatohepatitis (NASH) or with evidence of advanced fibrosis (see below).

Natural History of NAFLD/NASH

Nonalcoholic fatty liver disease is a spectrum of liver diseases. Although nonalcoholic fatty liver has a negligible risk of progression, patients with NASH often develop cirrhosis or hepatocellular carcinoma. Hepatic fibrosis, portal inflammation, diagnosis of NASH and ballooning are prognostic in their association with mortality in patients with NAFLD. Of these, fibrosis has emerged as the most important and significant predictor of mortality inpatients with NAFLD. In a meta-analysis and systematic review of studies that included paired liver biopsies at least one year apart the baseline distribution of fibrosis for stages 0, 1, 2, 3, and 4 was 35.8%, 32.5%, 16.7%, 9.3%, and 5.7%, respectively. On follow-up evaluation, 33.6% had progression of fibrosis, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. The estimated rate of progression by one stage of fibrosis was more rapid in patients with NASH simple steatosis and occurred at 7.1 vs. 14.3 years, respectively. In a multinational longitudinal study of patients with NAFLD over a median of 12.6 years, fibrosis stage, but not other histologic features of steatohepatitis, was associated independently with long-term overall mortality, liver transplantation, and liver-related events. Patients with fibrosis, regardless of steatohepatitis or NAFLD activity score, had shorter survival times than patients without fibrosis.

Associated Metabolic Complications

The association between type 2 diabetes and fatty liver disease was explored recently in a proof-of-concept feasibility study. Adult patients (n=100) in a primary care setting in San Diego were screened for NAFLD and advanced fibrosis using non-invasive magnetic resonance imaging (MRI) to estimate the hepatic proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) to estimate hepatic stiffness. The prevalence of NAFLD was 65% with 7% having advanced fibrosis; one patient was found to have a primary hepatocellular carcinoma.

Diagnosis and Risk Stratification

While ultrasound is a widely available, inexpensive and radiation-free method for evaluating the presence of steatosis it is operator-dependent and does not provide information regarding hepatic fibrosis. Computed tomography provides an objective evaluation of the presence of steatosis. However, CT is more expensive than ultrasound and exposes the patient to radiation making the technique unsuitable for repeated imaging. As in the case of ultrasound, CT cannot distinguish uncomplicated steatosis from fibrosis. Magnetic resonance imaging (MRI) does not involved exposure radiation and can therefore be used for follow-up studies but is expensive. ^{1}H-magnetic resonance spectroscopy (MRS) accurately quantifies hepatic steatosis and is operator-independent. Ultrasound or MRI elastography offers a non-invasive assessment of fibrosis indicated by the presence of hepatic stiffness. Models with improved accuracy based on routinely available clinical and biochemical variables have recently been developed that predict the presence of biopsy-proven NASH and clinical fibrosis, respectively in patients with type 2 diabetes (Citations). These models can be used to guide clinical decision-making about the need for referral to hepatology services for consideration of liver biopsy.

Pathophysiology and Clinical Consequences

Current estimates indicate that development of hepatic fibrosis occurs in approximately 40–50% of patients with NASH. Progression of fatty liver to steatohepatitis may reflect an imbalance between pro-inflammatory and anti-inflammatory cytokines that trigger reactive oxygen species and intrahepatic lipid peroxidation. The degree of liver fibrosis dictates prognosis. While NAFLD carries a negligible risk of progression NASH with fibrosis carries a higher risk of progression of fibrosis and is associated with the complications of cirrhosis, hepatic decompensation, and hepatocellular carcinoma. In paired biopsy studies fibrosis is the most important predictor of mortality. NASH-related cirrhosis has become a major indication for liver transplantation. Accordingly, there is intense research interest in identifying reliable non-invasive biomarkers that can predict progression from benign hepatic steatosis to fibrosis and associated tissue complications. The aim is to replace needle biopsy, which carries clinical risks and is subject to sampling error, with non-invasive surrogates.

The etiopathogenesis of NAFLD/NASH remains incompletely understood. In addition to predisposing genetic factors obesity-associated insulin resistance is considered to be a cardinal and early metabolic defect. Impaired whole-body insulin action results in delivery of excess quantities of non-esterified (free) fatty acids to hepatocytes. This generates oxidative stress and lipotoxicity that promote activation of intracellular stress kinases and apoptosis or necroapoptosis. The damaged hepatocytes directly trigger inflammation and fibrogenesis, but can also lead to the emergence of fibrogenic progenitor cells.

NASH is also linked to inflammation in peripheral adipose tissue that involves mainly macrophages and humoral factors such as metabolically active adipocytokines.

Obesity-associated insulin resistance is an important risk factor for NAFLD. It has been proposed that NAFLD may be regarded as the hepatic manifestation of the metabolic syndrome and integral to the syndrome of ectopic adiposity. In turn, metabolic syndrome is a powerful risk factor for type 2 diabetes and cardiovascular disease. In support of the obesity/steatosis hypothesis, in addition to liver-related morbidity and mortality (fibrosis, cirrhosis, hepatocellular carcinoma) evidence is mounting linking NAFLD with an increased risk of cardiovascular disease. Current evidence supports the view that the association between NAFLD and metabolic syndrome may be bidirectional. Clinical cardiovascular manifestations of NALFD include atherothrombotic coronary heart disease, impaired cardiac function and structure (e.g. left ventricular dysfunction and heart failure), valvular heart disease

(e.g. aortic valve sclerosis) and arrhythmias (e.g. atrial fibrillation). An association between NAFLD with chronic renal disease has also been proposed. Emerging evidence suggests that NAFLD is closely associated other chronic diseases including renal impairment, sleep apnea, colorectal cancer, osteoporosis, and various endocrinopathies (e.g. polycystic ovary syndrome). The view of NALFD has been expanded to a multisystem disease that has major public health implications for the development and progression of cardiometabolic and other disorders.

Thus, NAFLD may be regarded as a precursor to both type 2 diabetes and cardiovascular disease. Recent data suggest that improvement of NALFD is associated with a reduction in the incidence of type 2 diabetes. Accordingly, effective therapies that prevent or reverse NAFLD would be expected to reduce long-term morbidity and premature mortality. Pharmacological interventions that target the metabolic initiators and promoters of hepatic steatosis and fibrosis represent a logical therapeutic approach. Elucidation of the metabolic pathways driving the development and progression of NAFLD/NASH has stimulated intense efforts to develop safe and effective pharmacological treatments.

The Need for Effective Pharmacotherapy

Comprehensive clinical practice guidelines for NAFLD/NASH have been published by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association which offer preferred approaches to the diagnostic, therapeutic and preventive aspects of care. Non-invasive scoring systems such as the NAFLD Fibrosis Score are recommended to identify patients who are at risk for steatohepatitis and advanced fibrosis.

Benefits on the development and/or progression of NAFLD have been reported. However, many patients are unable to adapt their lifestyles sufficiently to prevent or reverse NAFLD/NASH. Bariatric surgery may improve hepatic histology in the context of morbidly obese patients with NASH although randomized clinical trial data are currently lacking. Thus, adjunctive therapeutic approaches are required for patients at highest risk. Several classes of pharmacological drugs have been explored, or are currently in development. Many of these agents have actions on insulin action and/or lipid metabolism and vascular physiology (Table 1). Available treatments of proven benefit include vitamin E (for non-diabetic adults with biopsy-proven NASH) and pioglitazone (for biopsy-proven NASH). However, therapeutic effects are generally modest and long-term risk-to-benefit equations remain uncertain; none is currently approved for this indication by the US Food and Drug Administration (FDA). Based on a recent direct and network meta-analysis, pentoxifylline and obeticholic acid improve fibrosis, and vitamin E while thiazolidinediones and obeticholic acid improve ballooning degeneration in patients with NASH.

A Collaborative Approach to Finding New Treatments

The discovery of a safe and effective pharmacological intervention for NALFD/NASH would have important implications for global public health. However, several aspects of the evaluation of novel drugs for NAFLD/NASH present major challenges to clinical investigators. These challenges may be summarized as follows:

- The complex pathophysiology of the NALFD/NASH disease spectrum
- Identifying suitable subjects for interventional studies including considerations pertaining to the heightened risk of NAFLD among certain ethnic groups
- Comprehensive non-invasive evaluation of hepatic pathology and cardiometabolic risk profiles

These challenges point to the need for close collaboration between investigators who bring together expertise in clinical hepatology and human metabolism/clinical pharmacology. This approach permits drug-induced improvements in intermediary metabolism to be correlated with histological changes in the liver. State-of-the art hepatic imaging and robust methods for quantifying metabolic fluxes, including insulin action on hepatic glucose production and quantification of de novo lipogenesis, are sensitive investigative tools. Few centers are able to offer this combination of methodologies along with the requisite research expertise. Ready access to a multiethnic population is an additional valuable resource.

Looking Ahead

We propose that a collaborative model of clinical research will help accelerate the clinical development of effective novel therapies for NAFLD/NASH. The identification of non-invasive predictive biomarkers should facilitate the development of safe and effective new drugs for NAFLD/NASH. A better understanding of the complex metabolic derangements that characterize NALFD/NASH will inform the identification of novel therapeutic targets. The challenges of conducting clinical trials in subjects with NALFD/NASH are expected to stimulate increased levels of collaboration between clinical hepatologists and investigators with expertise in human metabolism.

Table 1. Metabolic/cardiometabolic drugs that have been evaluated or are in preclinical or clinical development as treatments for NAFLD/NASH. Data from Clinicaltrials.gov, PubMed, and other sources in the public domain.

CLASS	EXAMPLES
Insulin sensitizers	Pioglitazone Rosiglitazone Metformin GFT505 (dual PPAR-α/δ agonist
GLP-1 receptor agonists	Exenatide Liraglutide
DPP-4 inhibitors	Sitagliptin MK-0626 Vildagliptin
SGLT-2 inhibitors	Remogliflozin
Lipid-modifying agents	Atorvastatin Pitavastatin Fenofibrate Ezetimibe Omega-3 fatty acids Polyunsaturated fatty acids Colesevelam

Anti-oxidants	Vitamin E
Insulin and insulin analogs*	Insulin glargine Intranasal insulin
11-β-HSD-1 inhibitors	RO5093191
Sex-hormone replacement	Testosterone undecanoate**
Probiotics	VSL#3
Anti-obesity agents	Orlistat
Anti-hypertensive agents	Telmisartan Losartan
Anti-inflammatory agents	Amlexanox PXS4728A
FXR agonists	Obeticholic acid GW4064 WAY-362450 NR1H4
ACC inhibitor	NDI-010976
Miscellaneous	Resveratrol Pentoxifylline Metadoxine Aramchol

PPAR – Peroxisome proliferator-activated receptor; GLP-1 – Glucagon-like receptor-1; DPP-4 – Dipeptidyl peptidase; SGLT – Sodium-Glucose Cotransporter-2; 11-β-HSD-1 – 11β-hydroxysteroid dehydrogenase type 1; FXR – Farsenoid X receptor; ACC – Acetyl-CoA carboxylase

*In patients with diabetes ** In adult men with late-onset hypogonadism

References and Further Reading

Ahmed M. Non-alcoholic fatty liver disease in 2015. World J Hepatol. 2015 June 18; 7(11): 1450-1459.

Angulo P, Kleiner DE, Dam-Larsen S Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Keach JC, Lafferty HD, Stahler A, Haflidadottir S, Bendtsen F. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;149:389-97.

Bazick J, Donithan M, Neuschwander-Tetri BA, et al. Clinical Model for NASH and Advanced Fibrosis in Adult Patients With Diabetes and NAFLD: Guidelines for Referral in NAFLD. Diabetes Care 2015;38:1347-55.

Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47-64.

Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005-23.

Doycheva I, Cui J, Costa EA, HookerJ, Hofflich H, Bettencourt R, Brouha S, Sirlin CB, Loomba R. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. Aliment Pharmacol Ther 2015; doi: 10.1111/apt.13405. [Epub ahead of print]

Hamilton G, Middleton MS, Heba ER, Sirlin CB. Imaging Techniques for the assessment of Ectopic Fat in Liver and Skeletal Muscle. In: Krentz AJ, Heinemann L, Hompesch M (Eds). Research Methods for Diabetes & Cardiometabolic Drug Development: Focus on early phase clinical studies. Springer. 2015.

Loomba R, Chalasani N. The Hierarchical Model of NAFLD: Prognostic Significance of Histologic Features in NASH. Gastroenterology 149:278–281.

Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313:2263-73.

Rinella ME, Loomba R, Caldwell SH, et al. Controversies in the Diagnosis and Management of NAFLD and NASH. Gastroenterol Hepatol (N Y) 2014;10:219-27.

Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology 2011;54:344-53.

Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015;13:643-54.

Singh S, Khera R, Allen AM, Murad MH, Loomba R. Comparative effectiveness of pharmacological interventions for non-alcoholic steatohepatitis: A systematic review and network meta-analysis. Hepatology. 2015 Jul 18. doi: 10.1002/hep.27999. [Epub ahead of print]

Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes & Endocrinology 2014.

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As Senior Research Fellow at ProSciento, Prof. Krentz's research involves investigator-initiated research in diabetes and cardiometabolic therapies. In addition to original articles, reviews and book chapters he has authored or edited a number of textbooks on diabetes and cardiovascular disease including and *The Metabolic Syndrome and Cardiovascular Disease* (2007), *Drug Therapy for Type 2 Diabetes* (2013) and *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development* (2015). He is Professor of Endocrinology & Metabolism at the University of Buckingham, UK. Prof. Krentz serves on the editorial boards of several scientific journals and is founding Editor-in-Chief of Cardiovascular Endocrinology.

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Dr. Hompesch's is a highly regarded expert in early phase clinical trial design for diabetes, obesity and related metabolic drug and device development. He is also a founder of ProSciento, the leading CRO exclusively focused on metabolic diseases and one of the few CROs actively conducting clinical research and biomarker validation studies using imaging and biopsy methods to detect progressive NASH in NAFLD and diabetes patients for therapeutic development. Dr. Hompesch is the author of more than 85 peer-reviewed publications and editorials and is a regularly invited speaker at medical conferences. He is also an editor and co-author of a new textbook *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development* (2015).

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