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The Genetic Epidemiology of Nonalcoholic Fatty Liver Disease: Toward a Personalized Medicine 467
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The understanding of the genetic bases of complex diseases such as non-alcoholic fatty liver disease opens new opportunities and challenges. This article explores new tools designed toward moving genomic data into clinical medicine, providing putative answers to more practical questions.

The Relevance of Liver Histology to Predicting Clinically Meaningful Outcomes in Nonalcoholic Steatohepatitis 487
Mangesh R. Pagadala and Arthur J. McCullough

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver disease. Nonalcoholic steatohepatitis (NASH), the more severe form of NAFLD, has an increased risk for progression to cirrhosis. The available data suggest increased morbidity and mortality among those patients with advanced histologic severity such as NASH and fibrosis. Despite the lack of a universally accepted histologic definition of NAFLD and inconsistency among pathologists regarding histologic findings essential to the diagnosis of NASH, a few studies have identified specific histologic findings (particularly fibrosis regardless of stage) that are able to predict NAFLD-related mortality as being most important.

Mechanisms of Simple Hepatic Steatosis: Not So Simple After All 505
Scott C. Matherly and Puneet Puri

Nonalcoholic fatty liver disease (NAFLD) is becoming an epidemic. Fat is typically stored in adipose tissue in the form of triglycerides (TGs). The deposition of TGs in the liver is the result of an imbalance between the amount of energy taken in and the amount used. This balance is maintained by a complex interplay between the dietary intake of nutrients, the hormonal response to the nutrients, and their effect on both the liver and adipose tissue. Disruption of this system is what leads to the development of steatosis and is the focus of this article.

A Myriad of Pathways to NASH 525
Soledad Larrain and Mary E. Rinella

Nonalcoholic steatohepatitis (NASH) is defined histopathologically by the presence of macrovesicular steatosis, cellular ballooning, and inflammation. NASH represents a complex multifactorial disease that typically occurs within the context of the metabolic syndrome. NASH lacks homogeneity, and other forms of NASH can present atypically. Less than 50% of
patients with NASH respond to pharmacologic treatment, which speaks to this heterogeneity. The authors discuss drugs, disease entities, and nutritional states that can cause or exacerbate underlying NASH indirectly through worsening insulin resistance or directly by interfering with lipid metabolism, promoting oxidative injury, or activating inflammatory pathways.

**Mechanisms of Disease Progression in NASH: New Paradigms**

Brittany N. Bohinc and Anna Mae Diehl

The incidence of nonalcoholic fatty liver disease is increasing at an astonishing rate in the US population. Although only a small proportion of these patients develop steatohepatitis (NASH), those who do have a greater likelihood of developing end-stage liver disease and complications. Research on liver fibrosis and NASH progression shows that hedgehog (Hh) is re-activated after liver injury to assist in liver repair and regeneration. When the process of tissue repair and regeneration is prolonged or when Hh ligand and related genes are aberrantly regulated and excessive, tissue repair goes awry and NASH progresses to cirrhosis and hepatocellular carcinoma.

**Can Nash Be Diagnosed, Graded, and Staged Noninvasively?**

Garfield A. Grandison and Paul Angulo

Nonalcoholic bland steatosis and nonalcoholic steatohepatitis (NASH) are stages in the spectrum of nonalcoholic fatty liver disease (NAFLD). NASH may progress to end-stage liver disease. Liver biopsy distinguishes between patients with NASH and no NASH and can stage fibrosis. Markers of hepatocyte apoptosis hold promise as noninvasive tests for NASH diagnosis. Several scoring systems that combine routine clinical and laboratory variables and some proprietary panels can assist in predicting fibrosis severity. Noninvasive imaging modalities are reasonably accurate available tools to determine severity of fibrosis in NAFLD, but none of them yet can replace liver biopsy.

**Is Nonalcoholic Fatty Liver Disease in Children the Same Disease as in Adults?**

Evelyn Hsu and Karen Murray

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children, and can present in toddlerhood. There is a differential distribution of NAFLD in children based on race and gender. The gold standard for diagnosis and classification of pediatric NAFLD is liver biopsy although ongoing studies aim to identify and define noninvasive investigations for pediatric NAFLD. Treatments that have been shown to be successful in adult NAFLD, such as insulin sensitizers and Vitamin E, have not been proven to be as definitively successful in children with NAFLD.

**The Cardiovascular Link to Nonalcoholic Fatty Liver Disease: A Critical Analysis**

Tommy Pacana and Michael Fuchs

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and can progress from simple steatosis to nonalcoholic steatohepatitis and finally to liver cirrhosis. NAFLD is considered
to be the hepatic manifestation of the metabolic syndrome because both share common features, which implicates a role of NAFLD in the development and progression of cardiovascular disease (CVD). The diagnosis of NAFLD deserves special attention in clinical practice for cardiovascular risk screening and surveillance strategies to allow for early targeted intervention in selected individuals at risk of future cardiovascular events.

**Psychological and Psychiatric Aspects of Treatment of Obesity and Nonalcoholic Fatty Liver Disease**  
Karen E. Stewart and James L. Levenson

Chronic illnesses incur a tremendous cost to American lives in dollars and quality of life. Outcomes in these illnesses are often affected by psychological, behavioral, and pharmacologic issues related to mental illness and psychological symptoms. This article focuses on psychological and psychiatric issues related to the treatment of obesity and nonalcoholic fatty liver disease (NAFLD), including available weight-loss interventions, the complex relationship between psychiatric disorders and obesity, and special considerations regarding use of psychiatric drugs in patients with or at risk for NAFLD and obesity. Recommendations for collaborative care of individuals with comorbid NAFLD and psychological disorders/symptoms are discussed.

**Management of Nonalcoholic Steatohepatitis: An Evidence-Based Approach**  
Suzanne E. Mahady and Jacob George

Nonalcoholic fatty liver disease (NAFLD) and its progressive form, nonalcoholic steatohepatitis (NASH), are an increasingly common cause of chronic liver disease in the developed world, with NASH projected to be the leading cause of liver transplantation in the United States by 2020. This review of NASH management addresses current data from the perspective of levels of evidence for therapeutic options in NASH, including lifestyle modification, drug therapies, and bariatric surgery. In particular, behavioral therapies to assist patients in adopting lifestyle changes are highlighted and a research agenda for future NASH management is presented.

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