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NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): METABOLIC MECHANISMS AND RISK OF PROGRESSION TO CIRRHOSIS

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disorder characterized by excessive fat accumulation in hepatocytes in the absence of significant alcohol consumption. It is strongly associated with obesity, insulin resistance, type 2 diabetes mellitus, and metabolic syndrome. NAFLD encompasses a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and eventually cirrhosis. Pathophysiology involves multiple metabolic mechanisms including insulin resistance, oxidative stress, lipid peroxidation, inflammatory cytokine production, and mitochondrial dysfunction. Early identification of at-risk individuals, non-invasive assessment of fibrosis, and targeted interventions are crucial to prevent progression. Therapeutic strategies focus on lifestyle modification, management of metabolic comorbidities, pharmacologic therapies under investigation, and emerging treatments targeting hepatic inflammation and fibrosis. This article reviews the metabolic mechanisms underlying NAFLD, risk factors for progression to cirrhosis, diagnostic strategies, and current and emerging therapeutic approaches.

Keywords

Non-alcoholic fatty liver disease, NAFLD, non-alcoholic steatohepatitis, NASH, insulin resistance, metabolic syndrome, liver fibrosis, cirrhosis.

Introduction

NAFLD has become the most common chronic liver disease worldwide, affecting approximately 25–30% of adults. The disease is closely linked to obesity, insulin resistance, type

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2 diabetes, dyslipidemia, and other features of metabolic syndrome. NAFLD is now recognized as a hepatic manifestation of systemic metabolic dysfunction.

The spectrum of NAFLD includes:

Simple steatosis – fat accumulation without significant inflammation

Non-alcoholic steatohepatitis (NASH) – fat accumulation with hepatocyte injury, inflammation, and variable fibrosis

Advanced fibrosis and cirrhosis – progressive scarring that may lead to liver failure or hepatocellular carcinoma (HCC)

Progression from simple steatosis to NASH and cirrhosis occurs in a subset of patients, highlighting the importance of early detection and intervention.

Pathophysiology

NAFLD pathogenesis is multifactorial and involves a complex interplay of metabolic, inflammatory, and genetic factors.

Insulin Resistance

Insulin resistance is central to NAFLD. Impaired insulin signaling in liver and peripheral tissues promotes increased free fatty acid influx into hepatocytes, de novo lipogenesis, and reduced fatty acid oxidation, leading to fat accumulation.

Lipotoxicity and Oxidative Stress

Excess hepatic fat triggers lipotoxicity, generating reactive oxygen species (ROS) and mitochondrial dysfunction. Oxidative stress induces hepatocyte injury, apoptosis, and activation of hepatic stellate cells, promoting fibrosis.

Inflammatory Cytokines

Adipose tissue dysfunction in obesity leads to release of pro-inflammatory cytokines, including TNF-α, IL-6, and leptin, which amplify hepatic inflammation and fibrosis.

Genetic and Epigenetic Factors

Variants in genes such as PNPLA3 and TM6SF2 influence susceptibility to NAFLD and progression to NASH and fibrosis. Epigenetic modifications also contribute to disease heterogeneity.

Clinical Features

NAFLD is often asymptomatic and detected incidentally through abnormal liver function tests or imaging. Common features include:

Mild fatigue or malaise

Hepatomegaly on physical examination

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Elevated liver enzymes (ALT, AST)

Patients with NASH or advanced fibrosis may present with signs of portal hypertension, jaundice, or complications related to cirrhosis.

Diagnosis

Diagnosis requires evidence of hepatic steatosis without significant alcohol intake or other causes of liver disease.

Non-invasive Assessment

Ultrasound – first-line imaging for detecting steatosis

Transient elastography (FibroScan) – evaluates liver stiffness to detect fibrosis

Biochemical indices – AST/ALT ratio, NAFLD fibrosis score, FIB-4 index.

Liver Biopsy

Liver biopsy remains the gold standard for distinguishing NASH from simple steatosis and for staging fibrosis, but it is reserved for selected patients due to invasiveness.

Management

Lifestyle Modification

Weight loss of 7–10% improves hepatic steatosis and histology

Diet rich in fruits, vegetables, and reduced saturated fat

Regular aerobic and resistance exercise

Management of Comorbidities

Optimizing glycemic control in diabetes

Treating dyslipidemia and hypertension

Managing obesity through behavioral interventions or bariatric surgery

Pharmacologic Therapy

Currently, no medications are specifically approved for NAFLD, but emerging options include:

Pioglitazone – improves insulin sensitivity and NASH histology

Vitamin E – antioxidant therapy in non-diabetic NASH patients

GLP-1 receptor agonists – reduce weight and hepatic fat

Investigational antifibrotic and anti-inflammatory agents are under clinical trials

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Discussion

NAFLD represents a metabolic liver disorder with systemic implications. Early detection in high-risk individuals with obesity, diabetes, or metabolic syndrome is essential to prevent progression to cirrhosis. Non-invasive biomarkers and imaging tools improve risk stratification and help avoid unnecessary biopsies. Comprehensive management addressing lifestyle, metabolic comorbidities, and emerging pharmacologic interventions is key to reducing liver-related morbidity and mortality. Public health measures targeting obesity and sedentary lifestyles are equally important.

Conclusion

NAFLD is a prevalent metabolic liver disease with a spectrum ranging from simple steatosis to cirrhosis. Insulin resistance, adipose tissue dysfunction, oxidative stress, and inflammation are central mechanisms driving disease progression. Early recognition, lifestyle modification, management of metabolic comorbidities, and emerging pharmacologic therapies are crucial to prevent cirrhosis and its complications. Multidisciplinary approaches and ongoing research into targeted therapies will continue to improve outcomes for patients with NAFLD.

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