NASH-LEADING CAUSE OF CIRRHOSIS

DR.GOUTAM KUMAR ACHERJYA

JR. CONSULTANT (MEDICINE)

UPAZILA HEALTH COMPLEX

BAGERPARA,JESSORE

BANGLADESH

Definition

Nonalcoholic steatohepatitis (NASH) is a liver disease characterized by the histological features of steatohepatitis in the absence of alcohol consumption.

NASH, particularly responsible for liver injury and fibrosis, is the result of a complex interplay between host and environmental factors.

Background

- Non-alcoholic fatty liver disease (NAFLD) is an universal disorder which is now considered as the most common liver disease in the western world.
- While non-alcoholic fatty liver disease due to central adiposity, obesity, insulin resistance, metabolic syndrome and type 2 diabetes is a very common clinical problem in our day-to-day clinical practice, the management of this disease is still in its infancy.

CONTD’

- Although initially benign, the disease can progress slowly from simple non-alcoholic steatosis (NAS) to non-alcoholic steatohepatitis (NASH) and subsequently to hepatic fibrosis, cirrhosis of liver and hepatoma.
- NASH is the bridging condition between steatosis and cirrhosis in the spectrum of nonalcoholic fatty liver disorders (NAFLD), was barely recognized in 1981.
- NASH could be present in one third of NAFLD cases.

EPIDEMIOLOGY

- Globally, the NAFLD prevalence rate is estimated to around 25%, with up to 70% of patients with NAFLD affected by NASH.
- In USA, NASH prevalence rate is 3-8% (approximately 6 million individuals).
- In UK, 2-5% population have NASH.
- NASH is common present in at least 20% of obese adults or children with or without type 2 DM in Asia-Pacific region.

PATHOPHYSIOLOGY

- Majority of patients with the metabolic syndrome develop steatosis, only a minority exhibit NASH or fibrosis.
- The initiating events in NAFLD are based on the development of obesity and insulin resistance, leading to increase hepatic free fatty acid flux.
- The imbalance between the rate of import/synthesis and the rate of export/catabolism of fatty acids in the liver leads to the development of steatosis.

CONTD’

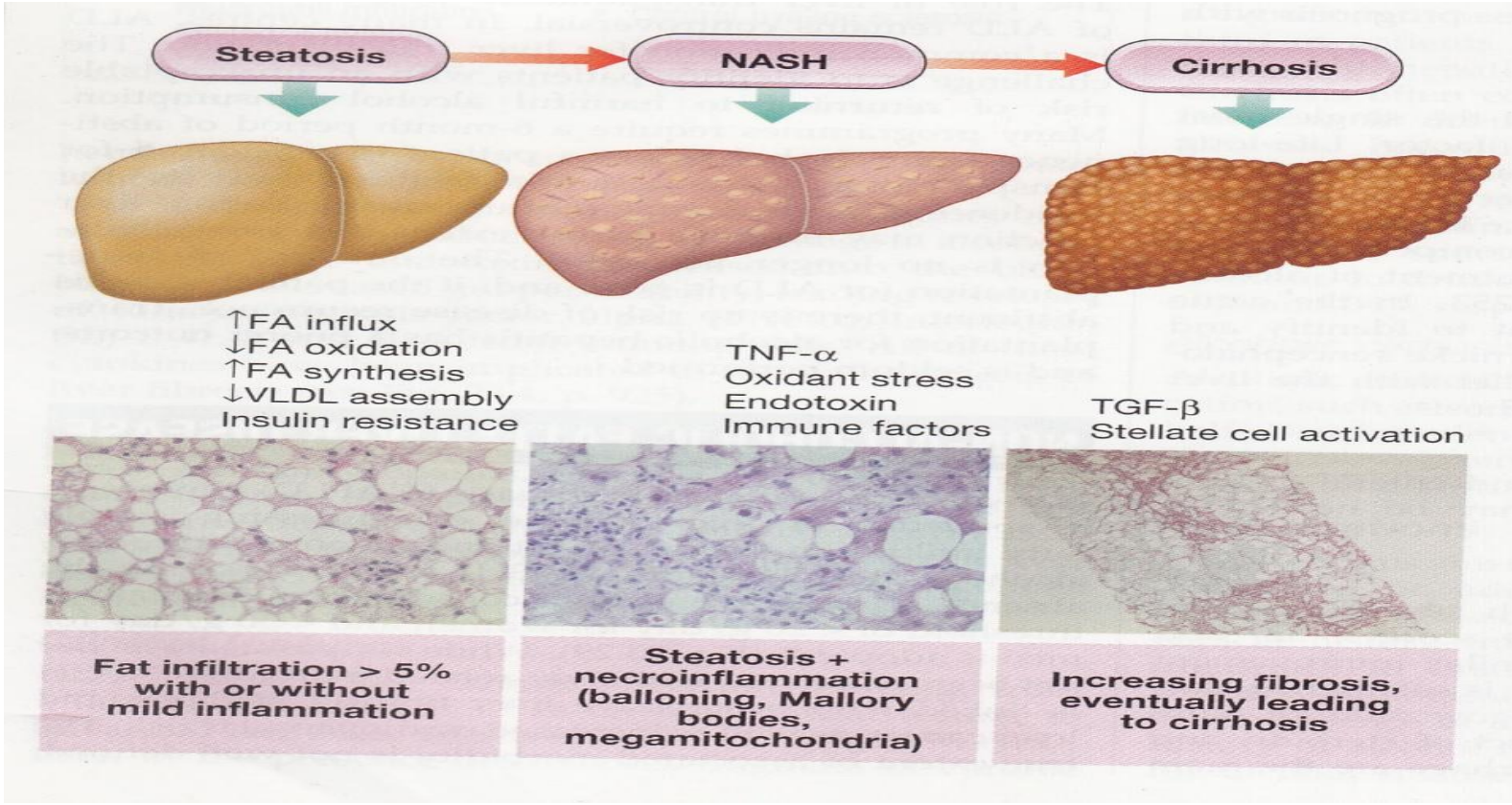
- A two-hit hypothesis has been proposed to describe the pathogenesis of NAFLD, the ‘first hit’ causing steatosis that then progresses to steatohepatitis if a ‘second hit’ occurs.
- Progression probably follows hepatocellular injury caused by a combination of several different ‘hits’ including:

CONTD’

- Oxidative stress due to free radicals produced during fatty acid oxidation.
- Direct lipotoxicity.
- Gut-derived endotoxin.
- Cytokine release(TNF-α etc.)
- Endoplasmic reticulum stress.

Immune-mediated hepatocellular injury and cell death, which leads to stellate cell activation and hepatic fibrosis.

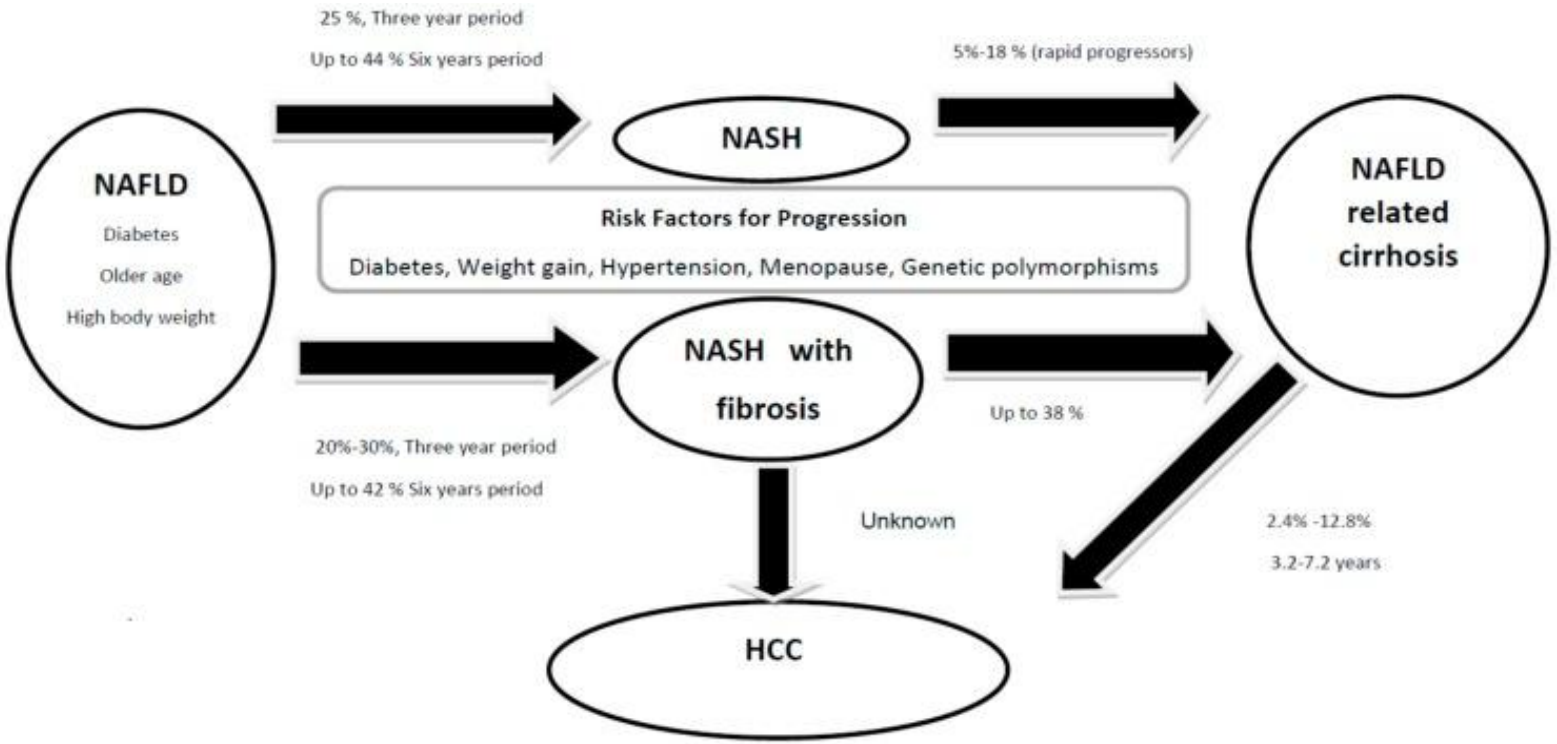
FEATURES OF NAFLD & NASH



Predictors of Progressive Fibrosis in Non-Alcoholic Steatohepatitis (NASH)

- Age: ↑ age to be consistently associated with more severe fibrosis in NASH patients.
- Sex: Men and post-menopausal women to have a higher risk of fibrosis compared with pre-menopausal women.
- Race and Ethnicity: More in Asian and Hispanic and less prevalence in Caucasians and African-Americans.
- Metabolic Features: Diabetes, obesity and hypertension.
- Genetic Polymorphisms: *PNPLA3* and *TM6SF2* genes.
- Histological Factors:

Progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) with or without fibrosis, cirrhosis, and hepatocellular carcinoma.



Wong V.W.-S *et al.*Disease progression of non-alcoholic fatty liver disease: A prospective study with paired liver biopsies at 3 years. Gut. 2010;59:969–974.

CLINICAL COURSE OF NASH

- The average age of NASH patients is 40-50 years.
- NASH- cirrhosis is about 50-60 years.
- The emerging epidemic of childhood obesity means that NASH is present in increasing numbers of younger patients.
- Risk factors for disease progression are age over 45 years, obesity (BMI > 30 kg/m^2) and hypertension.

INVESTIGATIONS

- ***Biochemical tests:***

  - ✓ ↑ed serum ALT and AST are modest.
  - ✓ AST:ALT ratio <1 in NASH.
  - ✓ AST:ALT ratio >1 in cirrhosis, meaning that steatohepatitis with advanced disease.
  - ✓ GGT: non-specific elevation.
  - ✓ ANA: low-titre in 20-30% of patients.
  - ✓ Ferritin: ↑ed.

CONTD’

- ***Imaging:***
  - ✓ Ultrasound: qualitative assessment of fat content. Sensitivity is limited when fewer than 33% of hepatocytes are steatotic.
  - ✓ Fibroscan: is very sensitive (70%) and specific (84%) in detecting the stages of hepatic fibrosis
  - ✓ CT, MRI or MR spectroscopy: greater sensitivity but cost effective.
- ***Liver Biopsy:*** gold standard for diagnosis and assessment of degree of inflammation and extent of liver fibrosis.

MANAGEMENT

- Many therapeutic agents have been tested, but still none approved specifically for NASH.
- Many novel compounds are being studied and will likely make combination therapy for NASH a reality in the future.
- So, we are at a new era in the management of NAFLD/NASH where increased awareness, early intervention and a combination of effective lifestyle intervention and pharmacological approaches will radically change the management of the disease.

CONTD’

- ***Non-pharmacological approach:***
  - ✓ A 7%-10% weight loss should be the goal in all overweight/obese NASH patient.
  - ✓ Dietary modification: Mediterranean diet.
  - ✓ Weight loss improves liver histology including hepatic fibrosis ≥10%.
  - ✓ Physical activity should be implemented because in improves metabolism
  - ✓ A sedentary lifestyle should be strongly discouraged.

CONTD'

- ***Pharmacological Treatment:***

  A lot of pharmacological agents (Antioxidants & Supplements, Anti-Hyperglycemic agents, Lipid lowering agents, Phosphodiesterase inhibitors, Bile acid/Farnesoid receptor pathway agents, Angiotensin II receptor antagonists) but none is currently licensed specifically for NASH theparpy. So, the cornerstone of medical management of NASH remains early detection and intervention.

FUTURE DIRECTIONS AND UNANSWERED QUESTION

A variety of new clinical trails are being conducted for the treatment of NASH.

- ✓ Antifibrotic drugs (Obeticholic Acid and Elafibranor) under development (in phase III clinical trails ended in 2017) are encouraging.

- ✓ Simtuzumab: Humanized monoclonal antibody with an immunoglobulin IgG4 isotype directed against human lysyl oxidase-like 2 (Phage II-ongoing, end in 2019)

CONTD’

- ✓ Aramchol: Inhibition of stearoyl coenzyme A desaturase 1 acitivity (modulates hepatic FA metabolism- Phage II clinical trail ongoing).
- ✓ Cenicriviroc: Immunomodulator and duel inhibitor of chemokine receptors CCR2 and CCR5, important players in the trafficking of monocytes/macrophages and other cell types (Phage II ongoing-end of 2017)

PROGNOSIS

- Premature mortality in NASH is related to both hepatic (cirrhosis and hepatocellular carcinoma) and extra-hepatic complications, largely cardiovascular diseases.

- The survival of patients with NASH cirrhosis falls markedly once decompensation occurs, with a median survival of approximately two years.

CONCLUSION

- ✓ Rising levels of obesity and T2DM, NASH prevalence will increase in the future.
- ✓ Despite considerable research and multiple clinical trails, at present no single pharmacological agent has achieved a clinical benefit.
- ✓ The combined efforts of academia, pharmaceutical industry and regulatory agencies will eventually bring the first approved therapy within a few years.

THANKS ALL