

Early life determinants of Non-Alcoholic Fatty Liver Disease and NASH

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Outline

- Definition NAFLD and NASH
- Magnitude of the problem
- Outline of disease process
- Early life determinants of disease
- Intervention and the way forward
- Conclusion
- References

Definitions

- **Fatty liver:** The accumulation of triglycerides and other fats within liver cells.
- **Steatosis:** $\geq 5\%$ of liver cells with micro- or macrovesicular fatty infiltration.
- **Non-Alcoholic fatty liver:** hepatic steatosis with no evidence of hepatocellular injury.
- **Non-Alcoholic Fatty liver disease:** the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.
- **Non-Alcoholic Steatohepatitis:** hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.
- **Cirrhosis:** process in which liver cells are destroyed and replaced by fibrous tissue surrounding islets of regenerative hepatocytes.

Why the interest in NAFLD?

- NAFLD becoming the most common cause of liver disease worldwide.
- Prevalence NAFLD in western countries now estimated at 20-30%, with a prevalence of 2-3% of NASH.
- In children NAFLD prevalence is 3-10%, rising up to 40-80% among the obese.
- Progression to NASH occurs in 10% of children. Disease manifests with more severe forms and progresses faster in children.

Why the interest in NAFLD?

- NAFLD considered by some to be the hepatic manifestation of the Metabolic syndrome.
- NASH may become a leading cause of chronic liver disease and transplantation.
- NAFLD may impact the QOL in children and has been shown to increase morbidity and mortality in adults.
- NAFLD also has extra-hepatic manifestations:
 - Cardiovascular disease
 - HCC
 - Chronic kidney disease
 - Colorectal cancer
 - DM II
 - Osteoporosis

Understanding NAFLD

Risk factors for NAFLD include:

- Obesity
- Hyperinsulinemia
- Hypertriglyceridemia
- Male gender
- Hispanics & Asians >Caucasians >African-Americans
- Genetics: SNPs like patatin-like phospholipase domain-containing protein-3 (*PNLA3*)

Understanding NAFLD

Pathogenesis

- The “Two Hit” Theory
 1. Fat deposition in the liver → insulin resistance and hyperinsulinemia with enhanced nonesterified fatty acid release from adipose tissue (lipolysis), increased *de novo* fatty acids (lipogenesis) and decreased β -oxidation.
 2. Oxidative stress and inflammation → mitochondrial dysfunction, proinflammatory cytokines, decreased adiponectin levels and hepatic apoptosis.

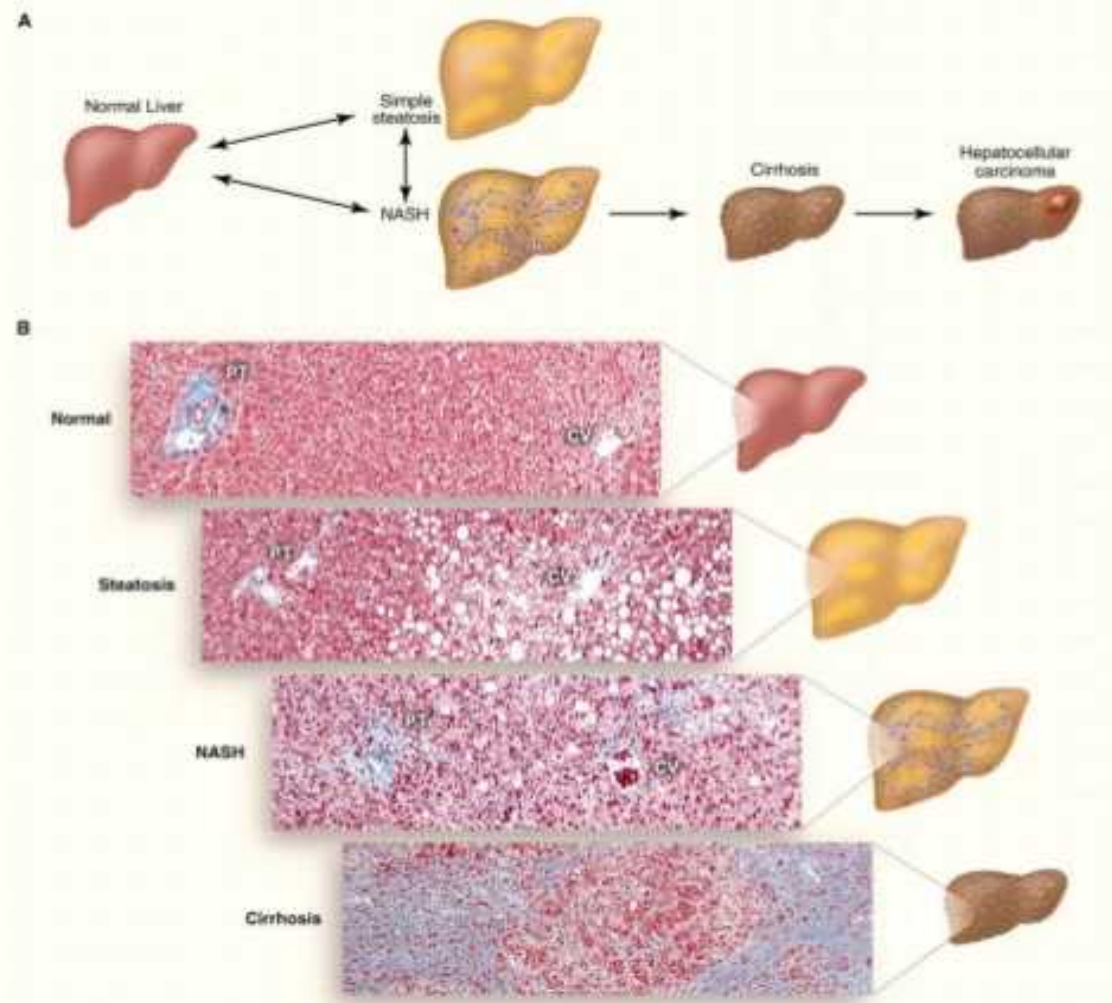
Understanding NAFLD

Diagnosis NAFLD

The diagnosis of NAFLD requires that

- (a) there is hepatic steatosis by imaging or histology,
- (b) there is no significant alcohol consumption,
- (c) there are no competing etiologies for hepatic steatosis,
- (d) There are no co-existing causes for chronic liver disease.

Understanding NAFLD-Histology



Cohen, et al, Human Fatty Liver Disease: Old Questions and New Insights, Science, June 2011.

Understanding NAFLD- Radiology

- Abdominal U/S: diffuse increase in hepatic echogenicity, or “bright liver”
- CT scan: reduced signal intensity in areas of fat deposition
- MRI and MRS
- Elastography esp. Fibroscan

Other diagnostic workup

- LFTs
- Fasting glucose
- Fasting cholesterol and triglycerides
- Fasting insulin levels
- Tests to r/o other causes of hepatic steatosis: caeruloplasmin, autoimmune antibodies, Hepatitis B & c, etc.

Understanding NAFLD- Treatment

1. Treatment of obesity → lifestyle changes including diet and exercise, to reduce weight by at least 5%.
2. Pharmacologic therapy:
 1. Improve insulin sensitivity: Metformin, Glitazones, ARBs
 2. Lipid lowering agents: clofibrate, gemfibrozil
 3. Hepatoprotective agents: USDA
 4. Anti-oxidants: Vit E, N-acetylcysteine
 5. Anti-TNF α : Pentoxifylline
 6. N-3 polyunsaturated fatty acids
 7. Probiotics/Synbiotics: *Lactobacillus rhamnosus* strain GG

Early Life Determinants of NAFLD

BUT FIRST....

Infant health is influenced by

- Maternal (and ?paternal) health and weight
- Genetics
- Epigenetics
- Gestation at birth and weight
- Infant feeding practices

Maternal Factors influencing development of NAFLD

- Maternal pre-pregnancy BMI
- Maternal weight gain in pregnancy
- Gestational DM
- ? Maternal intestinal microbiota
- Maternal nutritional deficiencies → Vit B12

Genetics in NAFLD

- PNPLA3: influences fatty acid deposition in the liver
- MBOAT7: influences secretion of VLDL in liver and gut
- ApoC3
- HFE: influences inflammation
- Genes influencing obesity and insulin resistance

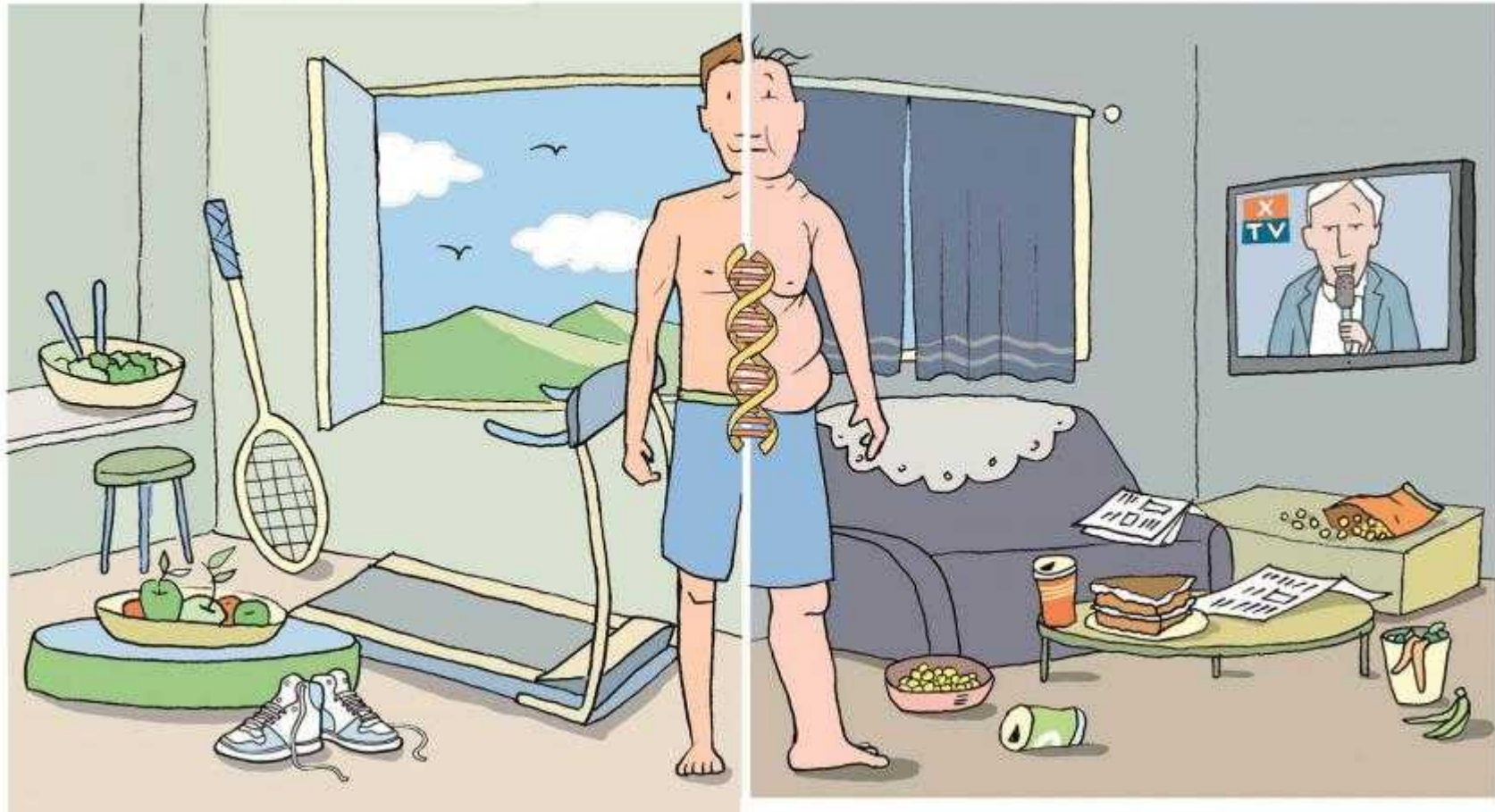
Epigenetics in NAFLD

Definition: the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.

This can be done through

- DNA methylation which allows genes to be expressed or not
- Histone modification which allows DNA to be “read” or transcribed
- Expression of noncoding RNAs may silence expression of genes

Epigenetics in NAFLD



Infant factors

- Low birth weight
- Large for gestation
- Rapid weight gain in early infancy
- Breastfeeding vs formula feeding
- Infant sleeping habits

Early childhood behaviour and nutrition

- High glucose and fructose rich foods
- Trans-fats
- Sedantary lifestyles

What's the way forward with NAFLD?

- Weight loss strategies
 - GUT microbiota manipulation
 - Change ratios of Firmicutes:Bacteroidetes
 - Decrease fat, protein and CHO intake
 - Prebiotics (fructans) and probiotics (Lactobacillus)
 - Improve the practice of exercising
- Improve screening of at risk individuals
 - women in reproductive age
 - Family members of index cases
 - At risk segments of the population

What's the way forward with NAFLD?

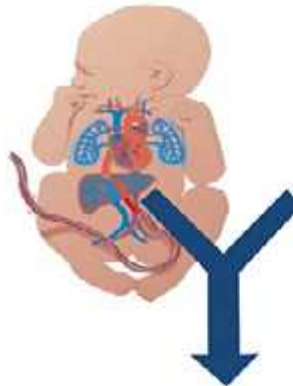
- Improve methods to detect progression of NAFLD to NASH
 - TNF α , IL-6, PTX-3, Ferritin
 - Markers of apoptosis – CK18
 - AST/platelet ratio index
 - Scoring systems

Conclusion



- Pre-gravid obesity
- Excess weight gain
- Inflammation
- Excess lipids/glucose

↓
 Insulin resistance
 Increased fuel to fetus



Other factors

- Maternal microbiome transfer to neonate
- Placental inflammation

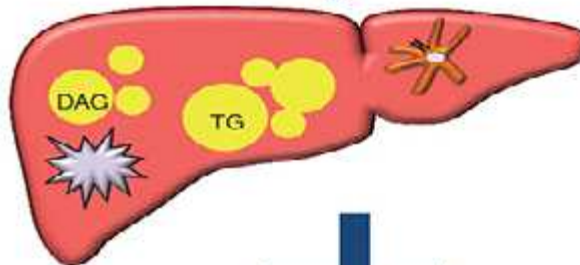
Fetal liver—a “first hit?”



- Hepatic fat accumulation
 Oxidative damage
 Mitochondrial dysfunction (sirtuins)
 Kupffer cell priming
 Epigenetic changes

- ↓
- Postnatal Western, high-fat diet
 - Genetic polymorphisms?
 - Environmental or dietary factors?

Childhood “second hit”



- Ongoing fat accumulation
 Increased *de novo* lipogenesis (SREBP1C)
 Reduced FA oxidation (PPAR α)
- Hepatocellular injury
 Kupffer cell activation
 Stellate cell activation
 Hepatocyte apoptosis
 Oxidative damage
 Endoplasmic reticulum stress

Hepatocyte injury
 Steatohepatitis



Fibrosis

Inflammation

References

1. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. 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. doi: 10.1002/hep.25762. PMID: 22488764
2. Vajro P, Lenta S, Socha P, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr.* 2012;54(5):700-713.

THANK YOU FOR LISTENING



QUESTIONS?

