
بسم الله الرحمن الرحيم

Non alcoholic fatty liver and Non alcoholic Steatohepatitis

By

Dr. Seham Seif

Definition

NAFL describe a common clinicopathological conditions characterized by significant lipid deposition in the hepatocytes in patients without a history of excessive alcohol intake.

NAFL include the full range of histological in this condition varying from steatosis alone to steatosis with inflammation, necrosis, fibrosis or cirrhosis (NASH).

Hepatic Steatosis represents one of the most common emerging liver diseases in Western countries. In the past it was mainly considered a harmless condition secondary to obesity and alcohol abuse. However, attention has recently shifted from innocent steatosis, to non-alcoholic steatohepatitis (NASH), a progressive fatty liver disease which may evolve to liver fibrosis and even cirrhosis.

What is non-alcoholic steatohepatitis?

- A syndrome of liver pathology that resemble alcoholic hepatitis, in non drinks (< 140gm ethanol 1week)
- Co-exit and may worsen other liver disease. Particularly chronic hepatitis C.
- > 70% patients have family history of type 2diabetes and on IGT or type 2 diabetes.
- > 85% patients have insulin resistance (metabolic syndrome) (diabetes, IGT and or insulin resistance, with two or more of arterial hypertension raised serum TG and or low serum HDL cholesterol, central obesity, microalbuminuria).

Standardized definition of NASH (Brunt et al., 1999)

- Steatosis of varying morphology
- Inflammation
- Hepato cellular degenerative changes
- Variable fibrosis

Risk factors for non-alcoholic steatohepatitis

1- DM particularly type2, family history of NIDDM, IGT: insulin resistance.

2- Obesity BMI > 27kg/m^2 in Asia , > 30kg/m^2 in Caucasians.

3- Central obesity: waist >97cm men, >85 women.

4- Hypertriglyceridmia, low HDL cholesterol.

5- > 45 years of age.

6- Rapid weight loss: after obesity surgery, fasting, starvation, cachexia, associated medical disorders.

7- Drugs (Methotrexate – Amiodaron – Estrogen – Nifidipen – Tamoxifen).

8- Occupational exposure (Petrochemical – Rapseed oil).

NASH why it is important?

- It is very common: mostly mild, overlaps with steatosis.
- NASH most common liver disease in western economies.
- Rising prevalence in Asia pacific region due to traditional life styles changes.
- Can cause end stage liver disease including some cases of cyptogenic cirrhosis.
- Overlapping disease parthenogenesis particularly fibrotic progression in hepatitis C.

Clinical Features and diagnosis of NASH

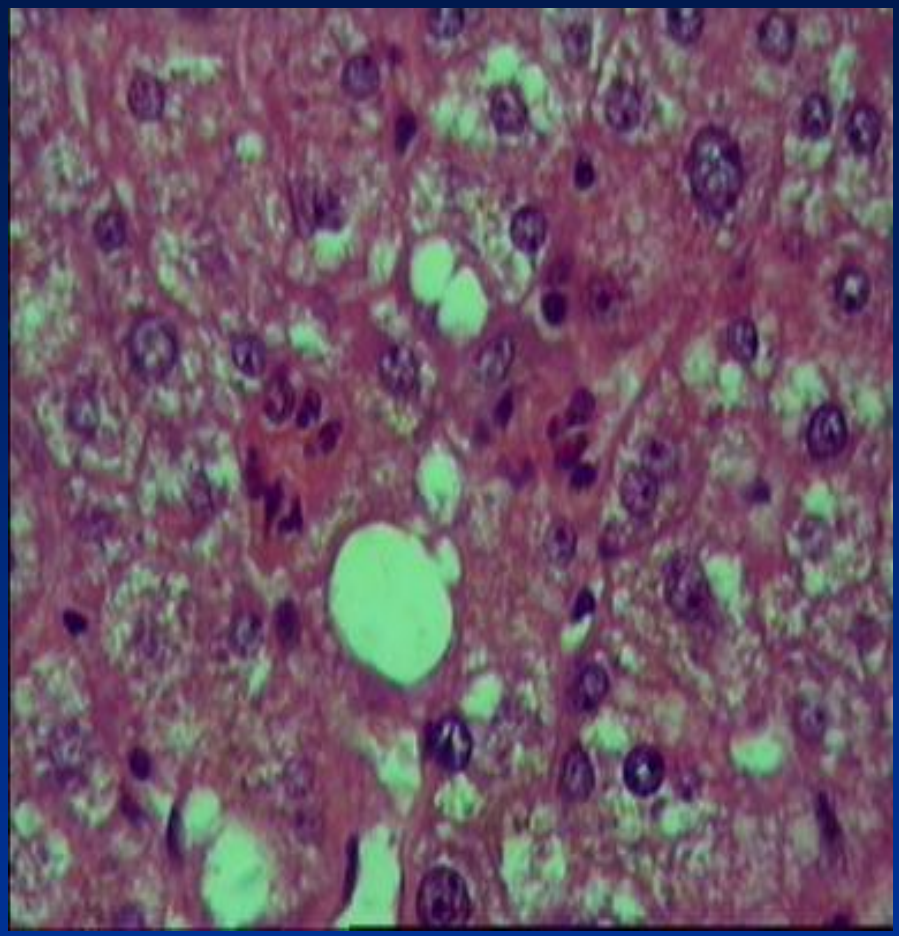
- **Clinical Features**
  - Asymptomatic.
  - Abnormal serum transaminases (mild↑AST and ALT and ratio AST/ALT < 1).
  - Hepatic discomfort and slight tenderness (common), pain (rare)
  - Hepatomegally
  - Clinical features of chronic liver disease (non-specific) decompensation (rare).

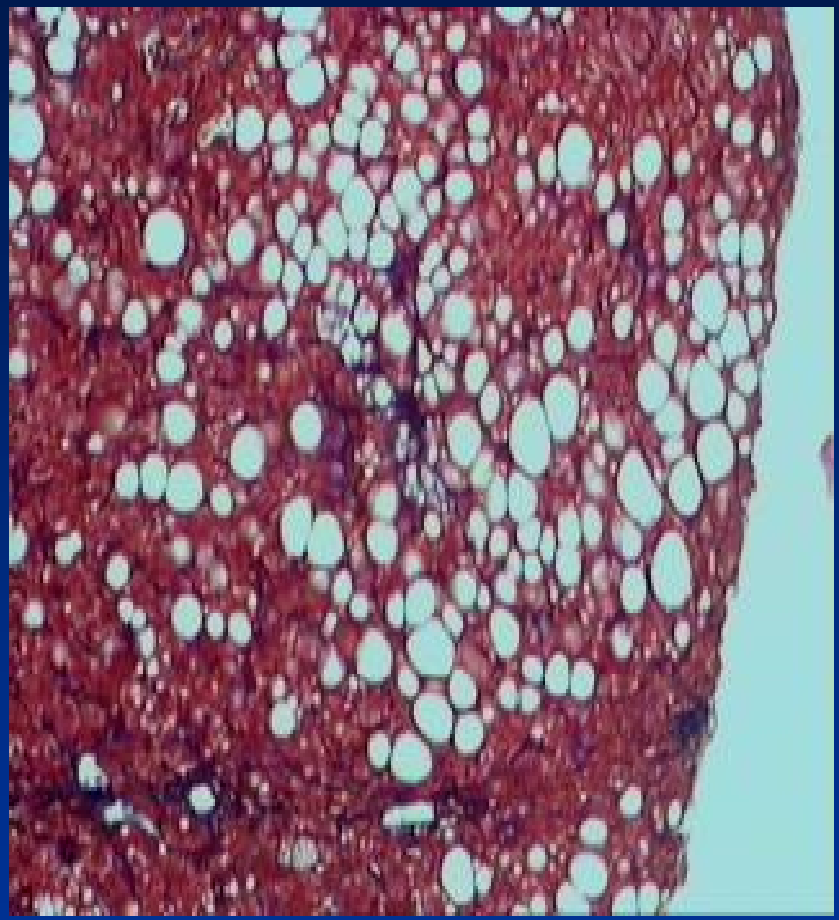
- **Investigation**
  - Exclude viral hepatitis autoimmune disorders, other metabolic disease.
  - Test for lipid disorders (Fasting serum TG, HDL, LDL cholesterol).
  - Hepatic imaging:
    - ultra-sonogram.
    - CT, radiolucency.
    - MRI- MR spectoscopy.
    - Liver biopsy.

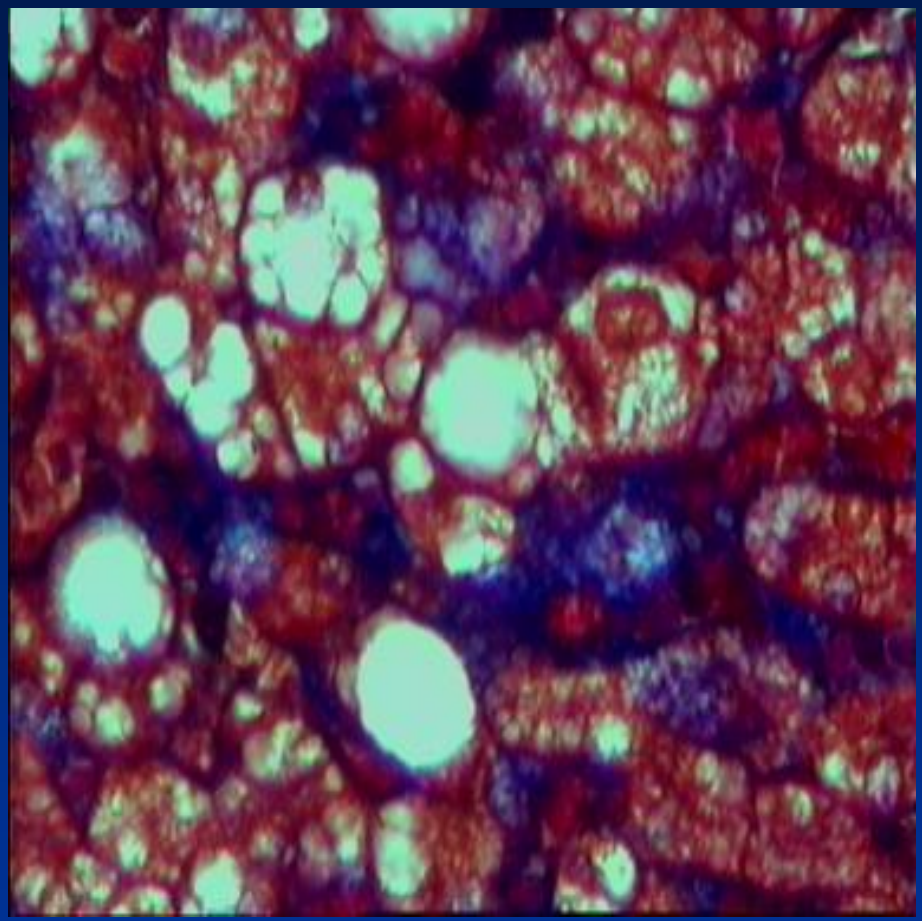
The histological features considered necessary for the diagnosis of NASH are

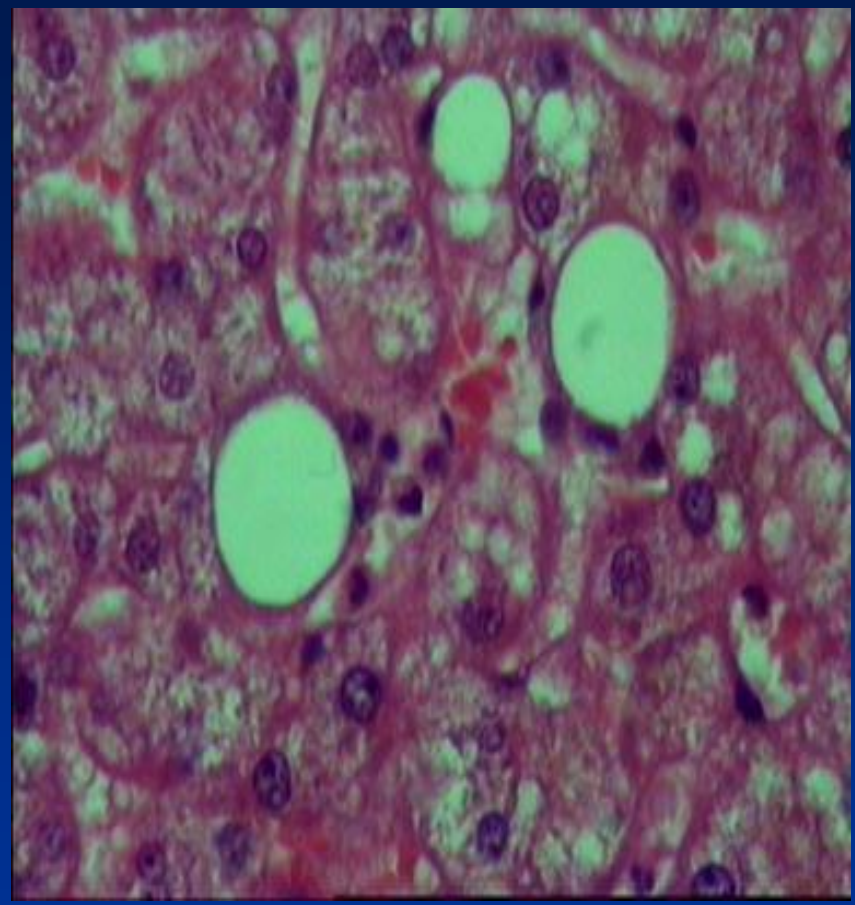
- **Steatosis of varying morphology**
  - predeminantley macro vesicular .
  - Mixed labulor inflammation.
  - Hepatocellular ballooning generally in zone3.
- **Other finding**
  - Perisinusridal fibrosis.
  - Mallory's bodies fat cyts glycogented hepato cellular nuclic in zone1.
  - Acido phil bodies in kuppfer cells.
- **Lipogranuloma** in the lobules and megamito chondria in hepatocytes.

- A grading system has been developed that characterized histologically the type of findings on liver biopsy. A system defines
- **Type1** as fat alone
- **Type2** fat + inflammation
- **Type3** fat with evidence of ballooning degeneration
- **Type4** fat with sinusoidal fibrosis and inflammatory infiltrates – Mallory hyaline bodies are present.









When to think of non-alcoholic steatohepatitis

- Unexplained elevation of liver tests (ALT, GGT: typically minor.
- Unexplained rubbey hepatonology
- Weight gain, expanding waistline
- Family history of: typ2 DM, Vascular/ heart disease, dyslipidemia, fatty liver.
- raised ferritin, not as result of iron storage or alcohol .
- people with HCV and non alcoholic steatohepatitis risk factors.
- Imaging changes as described above.

The initial hit is the retention of lipids within hepatocytes mostly in the form of TG is a prerequisite for the development of NASH. The primary metabolic abnormality leading to lipid accumulation (steatosis) could potentially result from insulin resistance and alteration in the uptake, synthesis, degradation or secretary pathway of hepatic lipid metabolism.

It is now clear that steatotic liver is more susceptible to oxidative stress and injury after injection of endotoxin.

However lipid accumulation may also be directly toxic to hepatocytes through the action of fatty acids which directly cause mitchondrial dysfunction.

Genetic predisposition

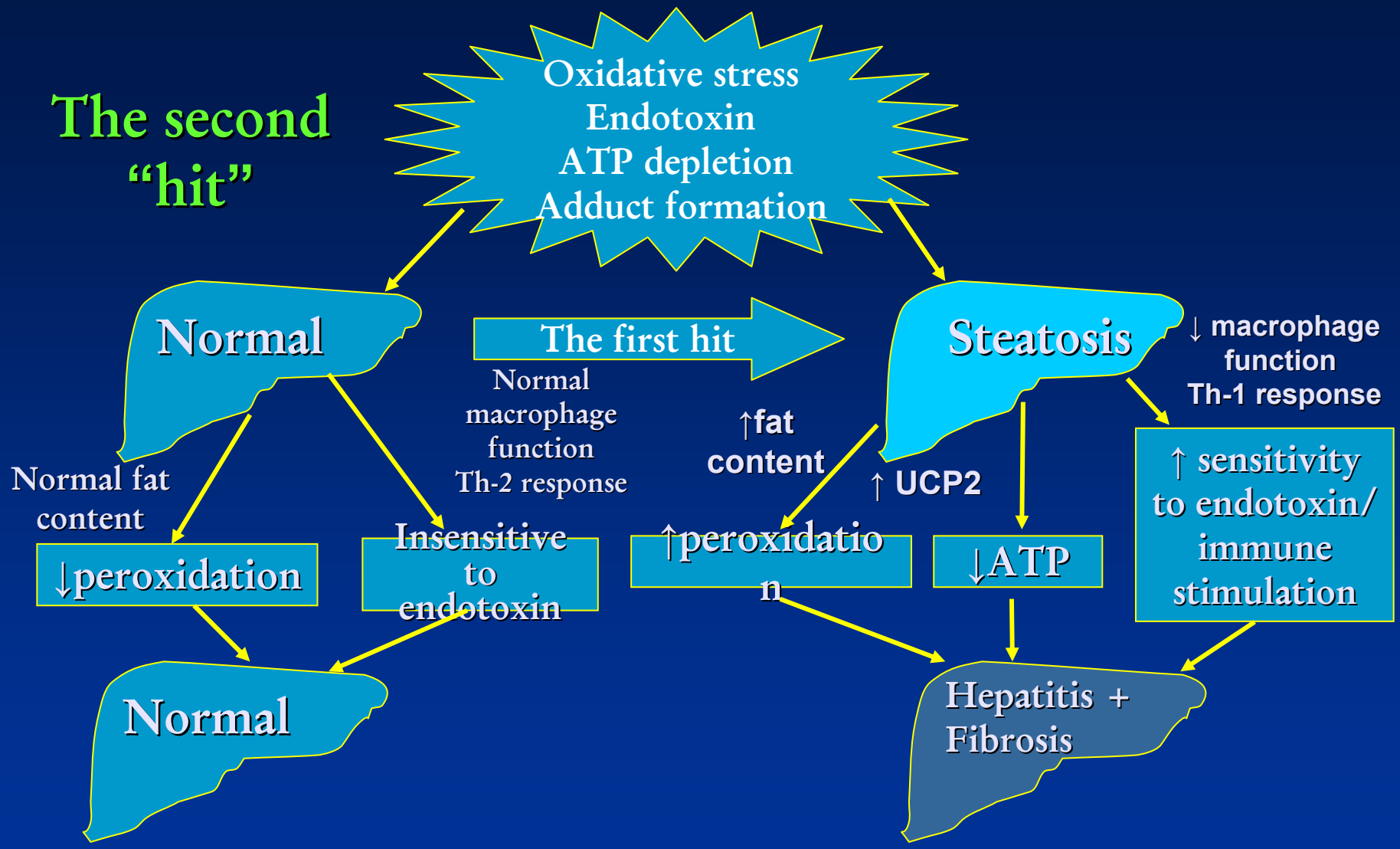
The gene that predispose to NASH undoubtedly include those which ordain insulin resistance and type 2 diabetes in time of caloric (energy) excess and inactivity.

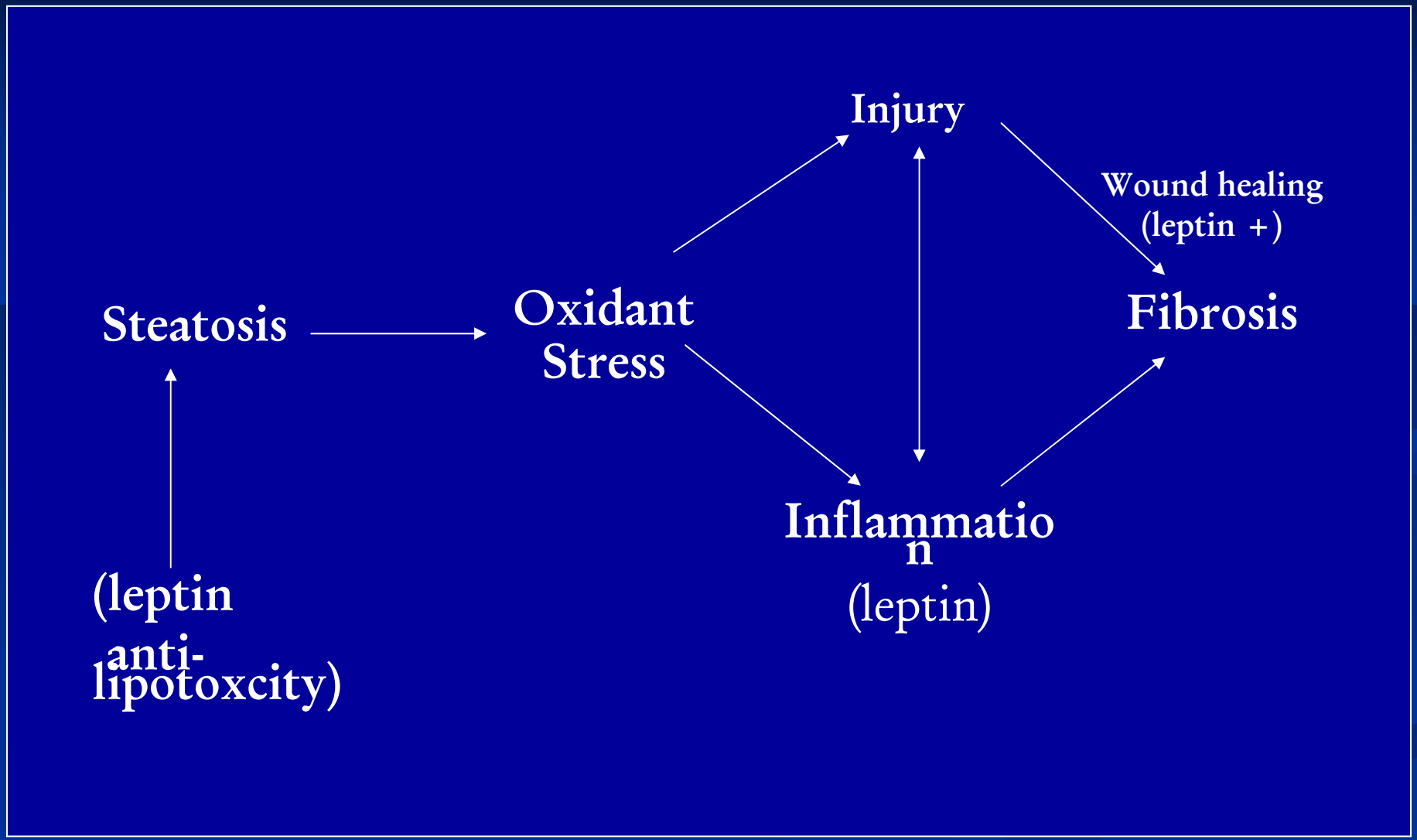
Role of oxidative stress

The second hit is oxidative stress which can cause liver injury for example by triggering apoptosis. Depletion of GSH also predisposes hepatocytes to cytotoxicly by tumor necrosis factor – α and incites inflammation via induction of nuclear factor- kappa B which up regulates cytocines and chemokines or through the direct chemetactic effects of hydroxynonenal, malonenaldehyde and other oxidized products of fatty acid degradation.

Fibro-genesis

Oxidative stress in the face of hepatic inflammation to induce and activate transforming growth factor-B may also play a key role in activating stellate cells to elaborate extracellulor matrix as part of general process of wound healing. The resultant hepatic fibro genesis has an obligatory dependence on leptin, leptin also required for appropriate liver regeneration as a part of wound healing, response to chronic hepatitis and other forms of liver injury.


The second "hit"
Oxidative stress
Endotoxin
ATP depletion
Adduct formation
Normal
The first hit
Steatosis
↓ macrophage function
Th-1 response
Normal fat content
↓peroxidation
Normal macrophage function
Th-2 response
Insensitive to endotoxin
↑fat content
↑peroxidation
↑ UCP2
↓ATP
↑ sensitivity to endotoxin/ immune stimulation
Normal
Hepatitis + Fibrosis


Injury
Wound healing
(leptin +)
Steatosis
Oxidant
Stress
Fibrosis
Inflammation
(leptin)
(leptin
anti-
lipotoxcity)

Current approaches to management

- **Prevention and non-drug management**
  - Correct insulin resistance
  - Correction of central obesity
  - Treat lipid disorders (diet, statins, gemfibrozil, probuchol)
  - Optimize blood glucose control.
  - If don't normalize alanine aminotransferase by 6 months, recommend liver biopsy
  - If 'warning' features for cirrhosis, recommend biopsy (unless imaging shows unequivocal cirrhosis)

Continue:

- **Value of exercise**
  - Stimulates insulin independent uptake of glucose in skeletal muscle (cyclic adenosine monophosphate/GLUT4).
  - Improves insulin sensitivity: reduce risk of type 2 diabetes by 58% in Finnish, USA diabetes intervention studies, even with minimal weight loss.
  - Enhances weight reduction without need for "crash" dieting.
- **Does drug treatment yet have a role?**
  - Metformin, thiazolidinediones (peroxisomal proliferator activator receptor-γ agonists) lower insulin resistance: may improve liver tests (? Sustained).
  - Antioxidants (vitamin E, betaine, probuchol, silymarin, S-adenosyl methionine)

Steatosis and chronic hepatitis C

- Hepatic steatosis is a characteristic histological finding in chronic hepatitis C virus (HCV) infection.
- However the mechanism for steatosis are unclear but it may related to host factors such as BMI and hyperlipidemia or virus specific pheromenon such as virus genotype which appears to be major determinant of hepatic steatosis in chronic hepatitis C infection irrespective to metabolic factors that usually correlate with fat deposition in liver.

Thank you