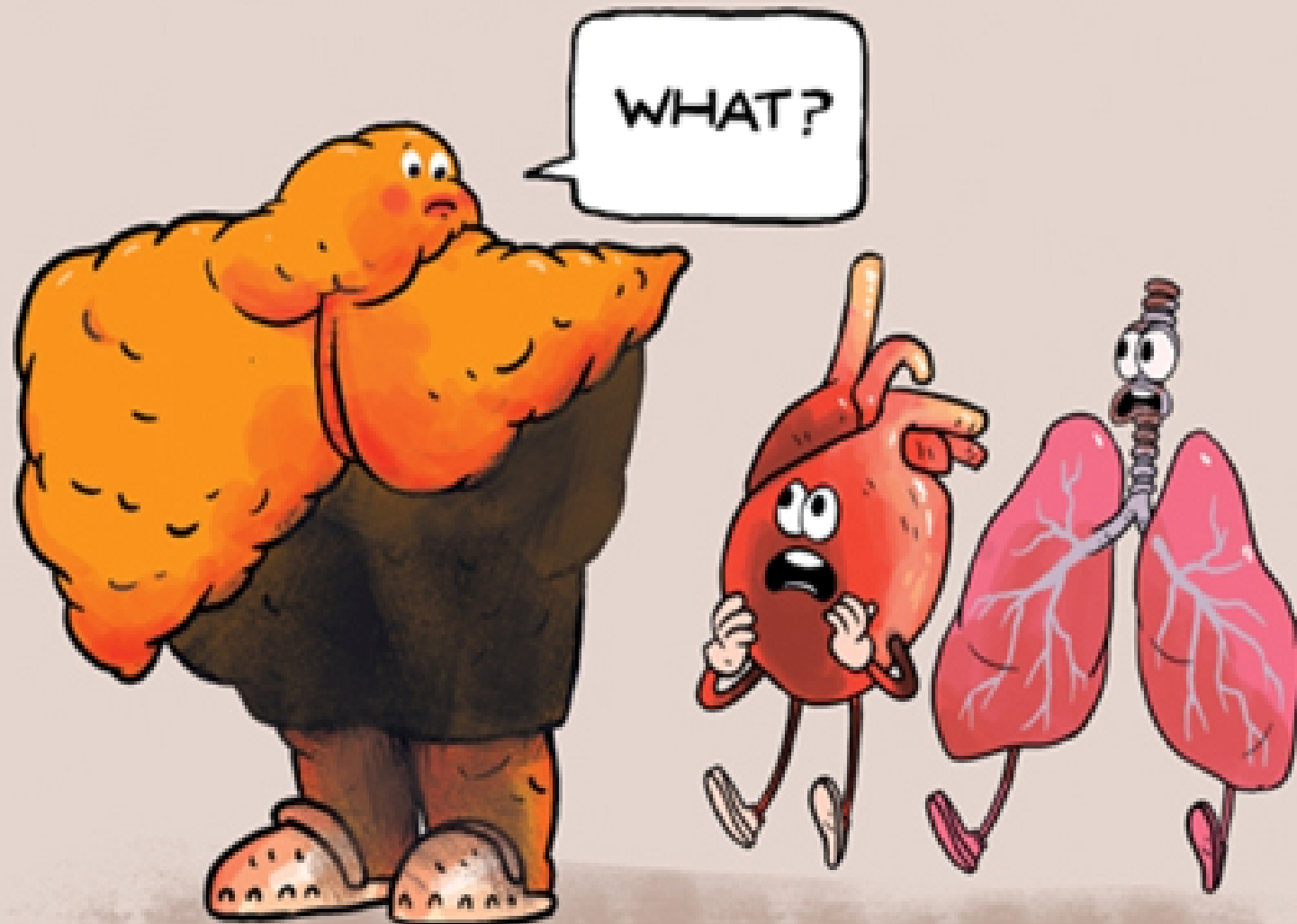


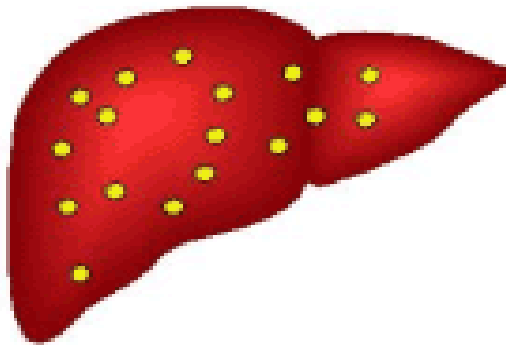
[Lonardo et al, Metabolism, 65\(8\): 1136-1150,2016](#)

FATTY LIVER CAN CAUSE SERIOUS DAMAGE TO OTHER ORGANS



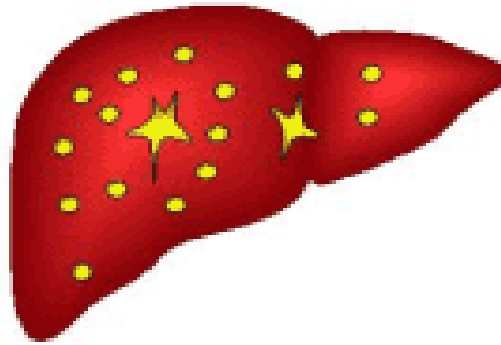
The Spectrum of NAFLD

Fatty Liver



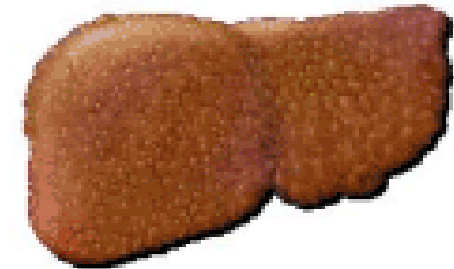
Fat
accumulates
in the liver

NASH

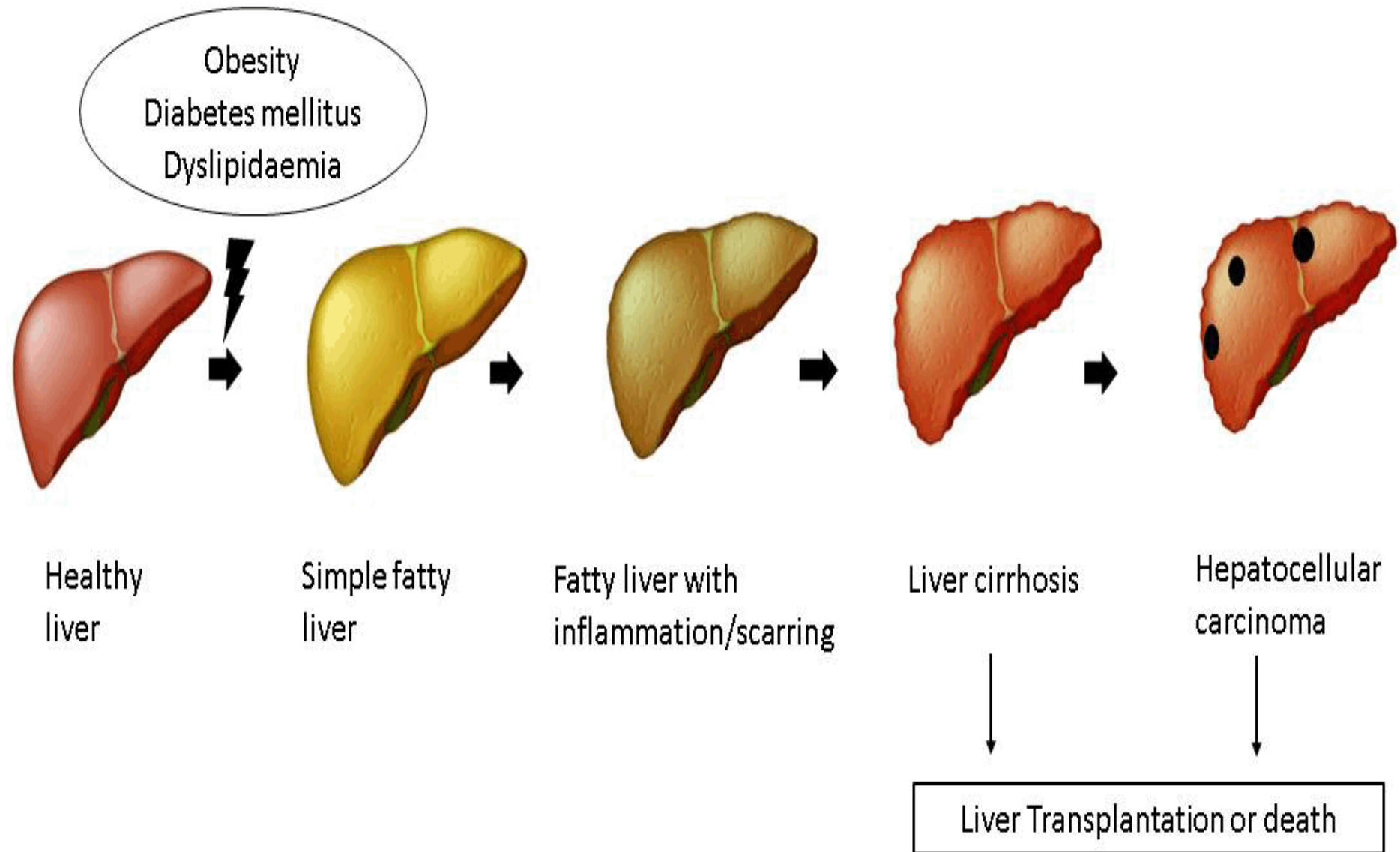


Fat plus
inflammation
and scarring

Cirrhosis



Scar tissue
replaces liver
cells



Adipose tissue accumulation and inflammation and T2DM

LCFAs, hyperinsulinaemia and inflammatory adipocytokines

LCFAs, DAGs, ceramides and/or DiPPA

TAGs

Lipid globule (steatosis)

- Lipotoxicity
- Oxidative stress
- Collagen matrix

Stellate and Kupffer cell activation

Genetic factors (for example, *PNPLA3* or *TM6SF2* genotypes)

Primary bile acids
Secondary bile acids

Intestine (dysbiosis and dietary changes, including high fat, high carbohydrate and high fructose diets)

Risk factors

- ↑ Insulin resistance
- ↑ Glucose production
- ↑ FGF21
- ↑ AHSG

- ↑ Triglycerides
- ↓ HDL cholesterol
- ↑ Small, dense LDL cholesterol
- ↑ Postprandial lipaemia

Cardiovascular disease and chronic kidney disease

- ↑ Angiotensinogen
- ↑ Endothelin 1
- ↑ TGFβ

- ↑ C-reactive protein
- ↑ IL-6
- ↑ TNF
- ↑ Reactive oxygen species

- ↑ Fibrinogen
- ↑ Factor VIII
- ↑ Coagulation factor
- ↑ PAI1

Risk factors

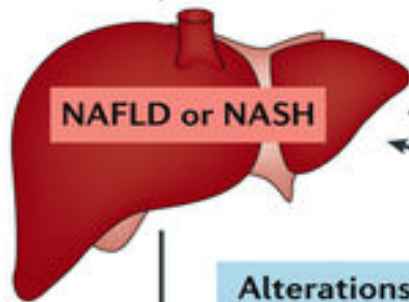
- Calorie intake
- Dietary and genetic factors
- Adipose tissue inflammation

↑ NEFAs

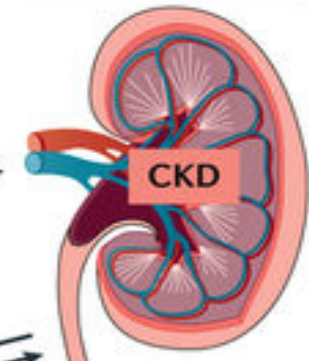
- Inflammation
- Adipokine dysregulation
- Hepatic insulin resistance
- Impaired insulin signalling

- Atherogenic dyslipidaemia (renovascular damage)
- Inflammatory factors, ROS and AGEs
- ↓ Adiponectin levels: reduced activation of AMPK (inflammation, fibrosis)
- Coagulation pathways and fibrosis pathways (activation of RAS and endothelial cells)
- ↑ Uric acid

- Inflammation
- Fibrosis



NAFLD or NASH



CKD

Alterations in gut microbiota

- Effects on glucose tolerance and inflammation
- ↓ SCFAs: lipogenesis and gluconeogenesis
- Production of toxic secondary bile acids (↑ intestinal permeability and effects on hepatic mitochondrial membranes)

↑ Uraemic toxins (TMAO, p-cresol, indole sulphate)

Other cardiorenal interactions

- RAS
- Uric acid
- Vascular calcification
- ROS

- Insulin resistance
- Gluconeogenesis

T2DM

Uraemic toxins

CVD

Serum Biomarkers for Nonalcoholic Fatty Liver Disease: Are We There Yet?

Liu K. et al . HEPATOLOGY, VOL. 65, NO. 1, 2017

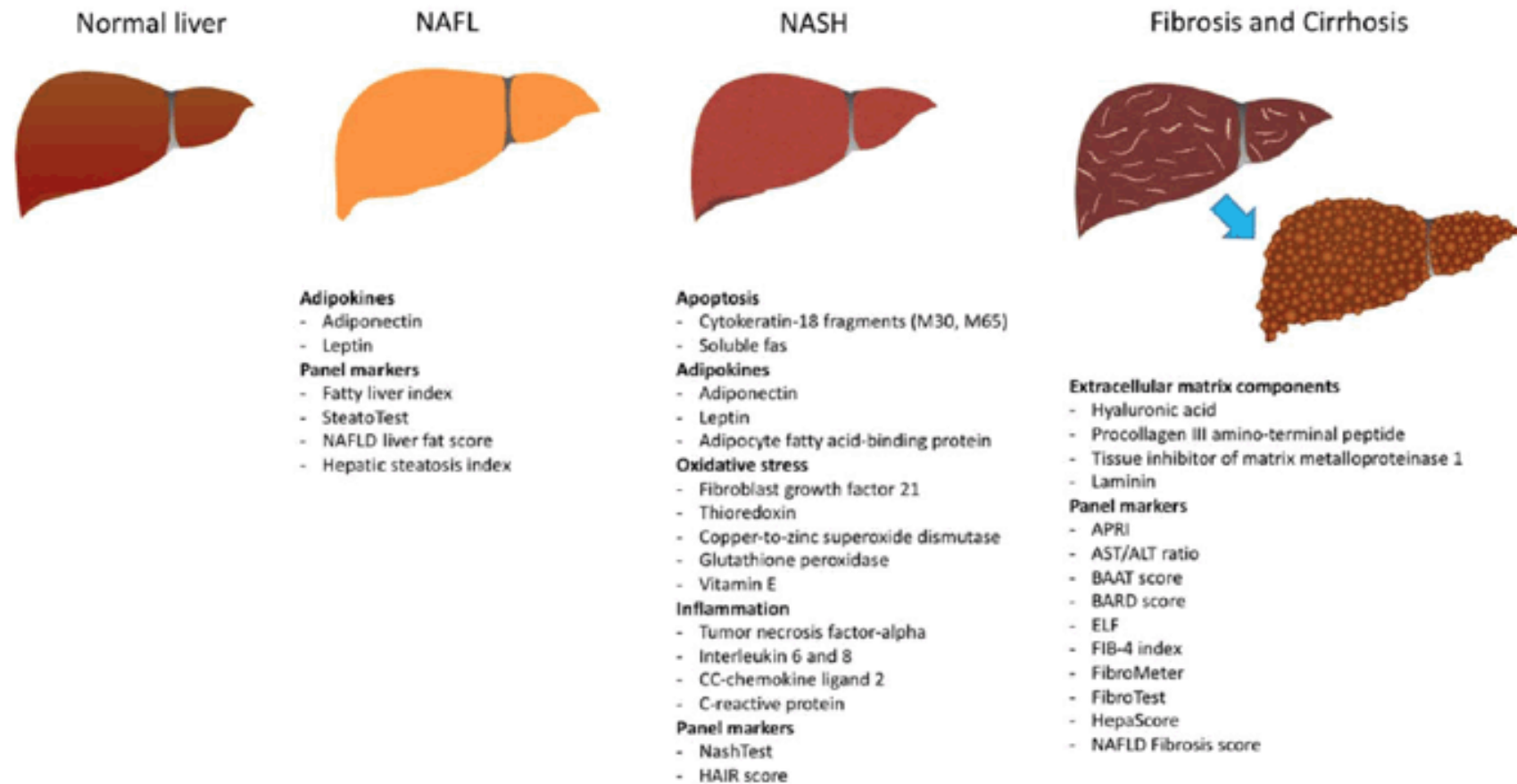


FIG. 1. Serum biomarkers across the NAFLD spectrum. Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase/platelet ratio index; AST, aspartate aminotransferase; BAAT, body mass index, alanine aminotransferase, and triglycerides; BARD, body mass index, alanine aminotransferase/aspartate aminotransferase ratio, and presence of diabetes; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; HAIR, hypertension, alanine aminotransferase, and insulin resistance.

How to Treat?

Insulin Sensitizers
Antihyperlipidemics



First Hit

Antioxidants
Cytoprotectants



Second Hit

→ Steatosis → NASH

Insulin resistance

↑ Fatty acids

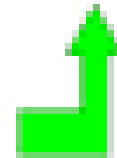


Weight Loss

Diet/Exercise

Lipid

peroxidation



Treatment options

Lifestyle modifications

Diet

Exercise with aim to lose 7-10% of body weight

Weight loss therapies

Orlistat

Bariatric surgery

Therapies for insulin resistance

Metformin

Glitazones

Glucagon-like peptide 1 (GLP1)

Lipid lowering agents

Statin

Emerging therapies

Cytoprotective and anti-oxidant agents

1) Ursodeoxycholic acid (UDCA)

2) Vitamin E

Angiotensin receptor blockers

Pentoxifylline

Novel therapies

Caspase inhibitors

Peroxisome proliferator-activated receptor (PPAR) agonist

Farnesoid X receptor agonists (obeticholic acid)