Non-Alcoholic Fatty Liver Disease

Contemporary Approaches to Assessment and Management

Jonathan Gabor MSc MD FRCPC SCH

Advances in Chronic Care CPD
University of Manitoba
February 2, 2018

Contextualize

NAFLD as the most common liver disorder with potential for significant health care burden

Understand

Key pathophysiologic concepts which inform clinical consequences and therapeutic options

Diagnose

Using a variety of approaches, simultaneously practical and thorough

Manage

NAFLD vigilantly and (for now) non-Rx, cognizant of new agents expected to enter the market

Objectives

Take Home Message …

Owing to its prevalence and predicted impact, NAFLD is a chronic disease with significant relevance to primary care. Interventions are multidisciplinary and specialist involvement is beneficial.

Local

Active Clinical & Research Field

presenter declaration

Disclosures and Bias Mitigation

Relationships with Commercial Interests

Grants: Pfizer, Servier

Ad Boards: Boehringer-Ingelheim

Honouraria: Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Novartis, Pfizer, Servier

Presenter: Jonathan Gabor

Research Support: none

Consulting Fees: none

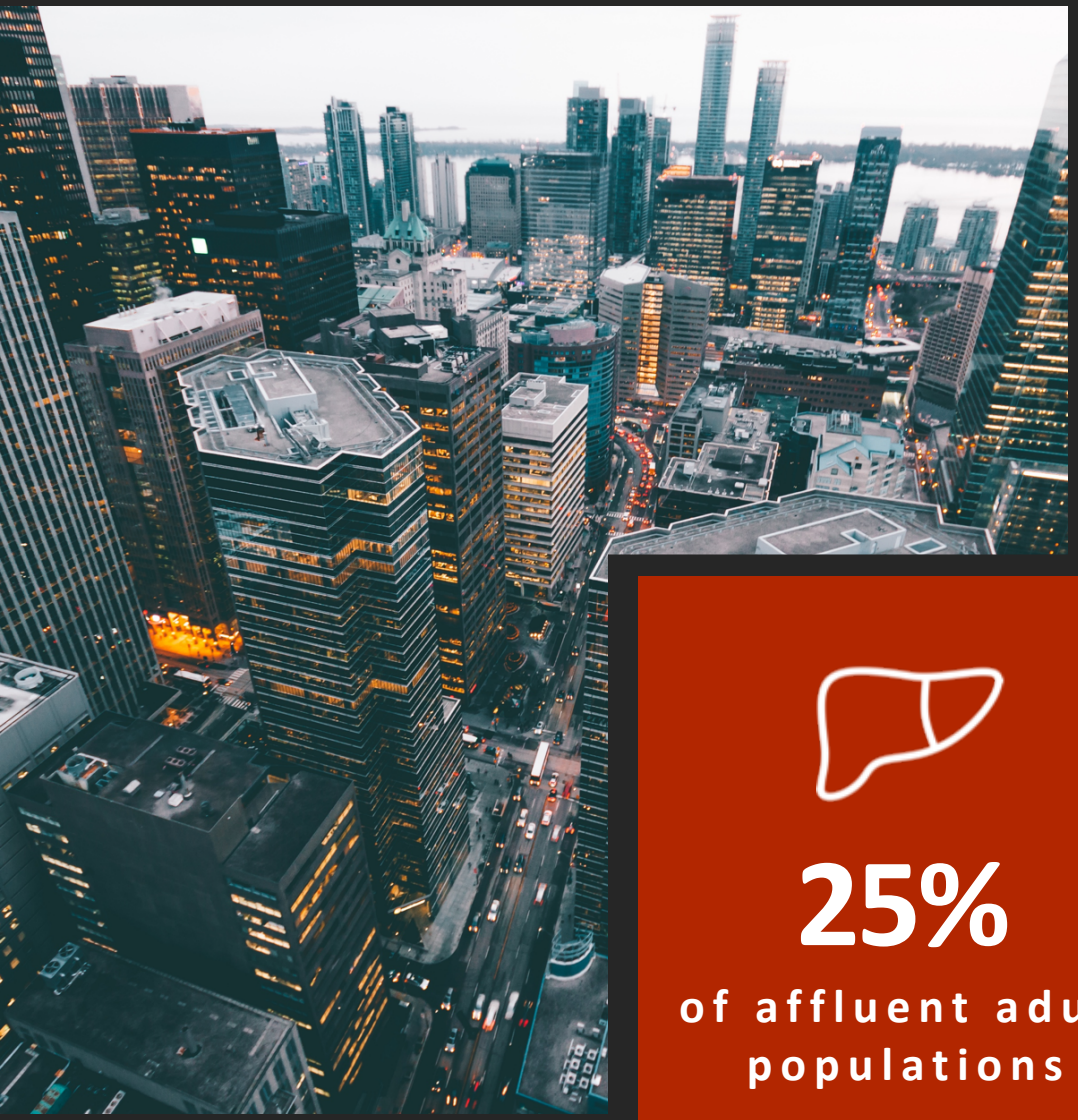
Other: none

Bias Mitigation

No commercial remuneration

No off-label recommendations

No endorsement of specific products



Non-alcoholic fatty liver disease is common

It is the most common form of chronic liver disease and the most common cause of abnormal liver enzymes, and (after Hepatitis C) the second-leading etiology of liver disease for adults awaiting transplantation

25%

of affluent adult populations

Prevalence
Parallels obesity and other components of metabolic syndrome

Challenges
diagnosis, screening, natural history, lack of approved Rx therapies

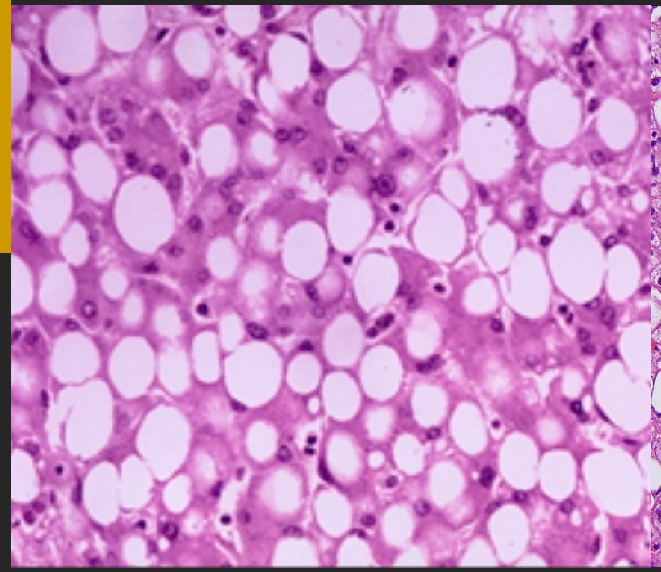
Transplant Trends
Most rapidly growing (and soon to be leading) transplant indication

Natural History

Progression of NAFLD

Simple Steatosis

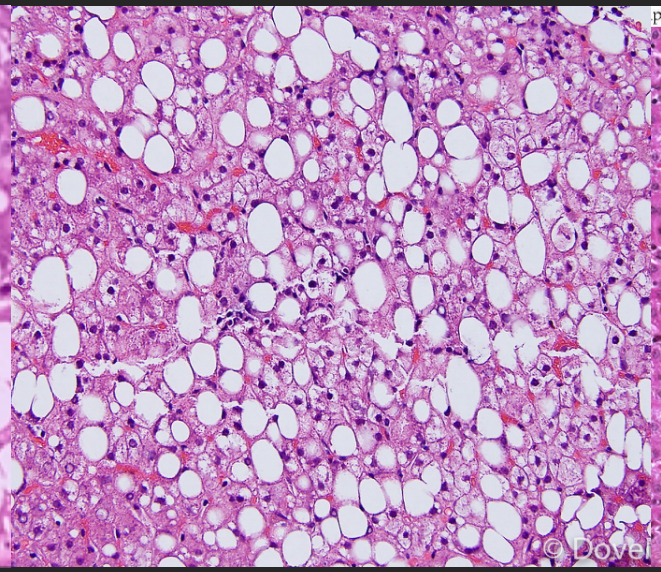
75-90% of cases
benign prognosis
no increase in mortality



Risk factor surveillance and modification

Steatohepatitis

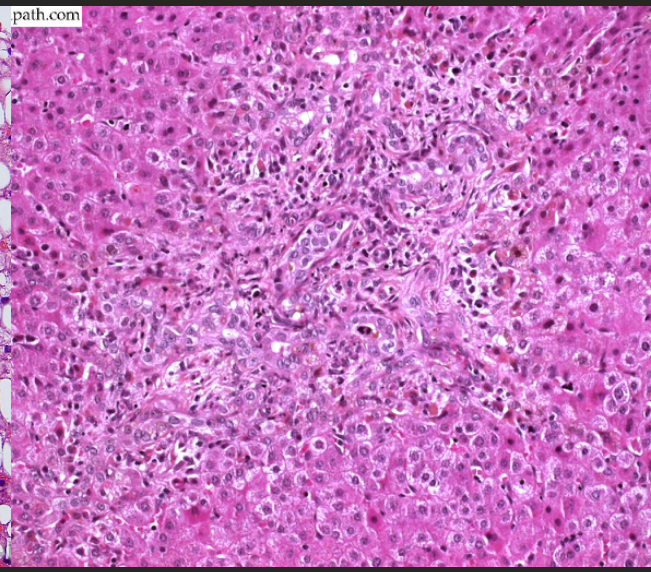
"NASH" - hepatocyte injury, inflammation, and fibrosis
25% of all NAFLD



Correlation with presence (and severity) of metabolic syndrome, and also CV risk

Cirrhosis

Extensive fibrosis and irreversible damage
25% of NASH patients



Cirrhotic complications, hepatocellular carncinoma, mortality

NAFLD Risk Factors

- Age
- Metabolic Syndrome
- Gender
- Dietary Factors
- OSA

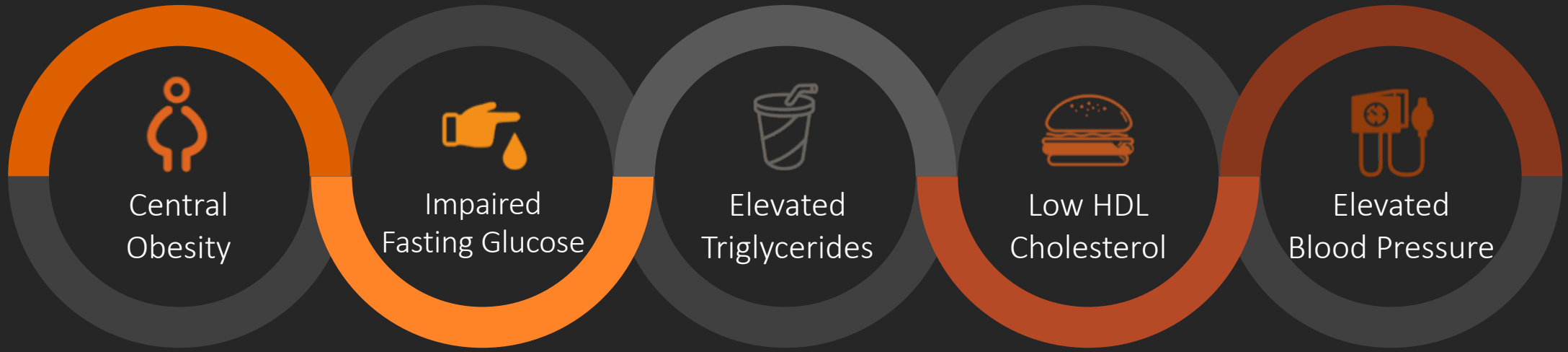
NASH is essentially a metabolic disorder

Covariates By the Numbers:

80%	70%	70%	45%	33%
Obese	HTN	Lipids	T2DM	MetS

The above support the concept that NASH is the hepatic consequence and manifestation of the metabolic syndrome (MetS), a systemic disorder of macronutrient energy regulation, processing and homeostasis, accompanied by ongoing inflammation and cellular injury with concomitant multi-organ risk

Features of the Metabolic Syndrome



Obesity
- WC >= 94 cm (M)
- WC >= 80 cm (F)
- Ethnic-specific

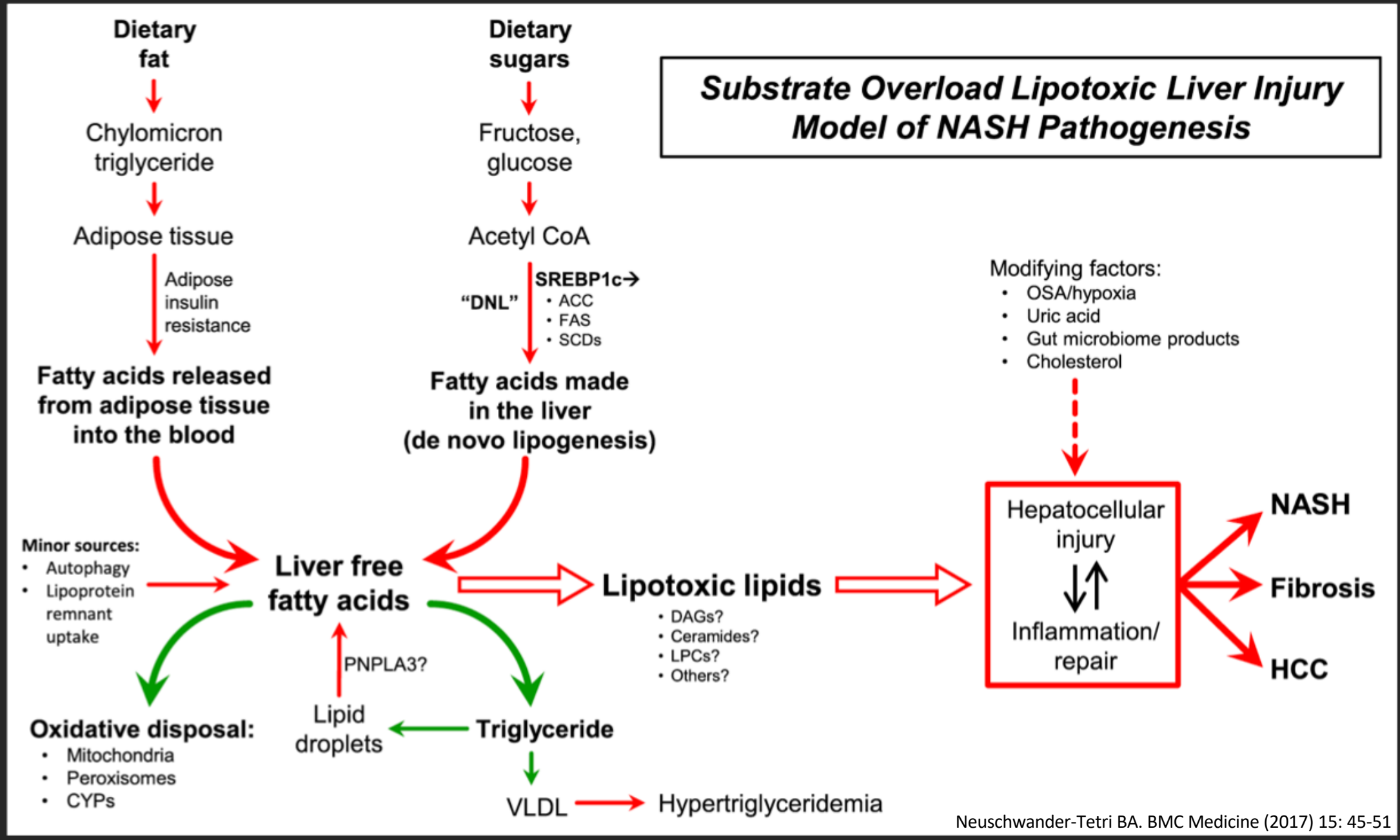
Hyperglycemia
- > 5.6 mmol/L
- Or on treatment

Dyslipidemia
- TG > 1.7 mmol/L
- Or on treatment

Dyslipidemia
- HDL < 1.0 (M)
- HDL < 1.3 (F)
- Or on treatment

Hypertension
- > 135/85 mm Hg
- Or on treatment

*at least three of five categories = diagnosis of metabolic syndrome



Neuschwander-Tetri BA. BMC Medicine (2017) 15: 45-51

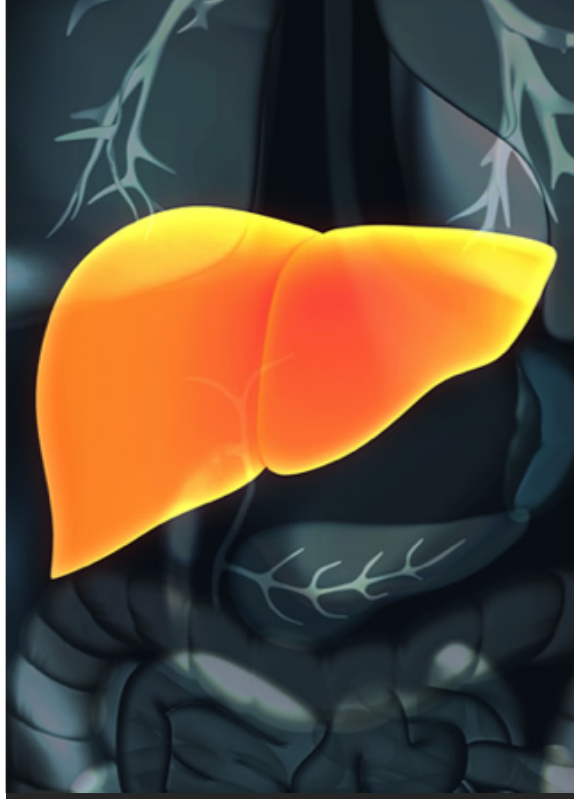
the diagnosis

Identifying NAFLD

A satisfying diagnosis if detection occurs in time for risk-mitigating intervention

Diagnostic Approaches

The approach to NAFLD is multimodal and iterative rather than automatic



Assessing severity is crucial to management and prognostication

Pearls and Challenges in the Diagnosis of NAFLD-NASH

Largely asymptomatic - ? screening

Over-reliance on liver chemistries

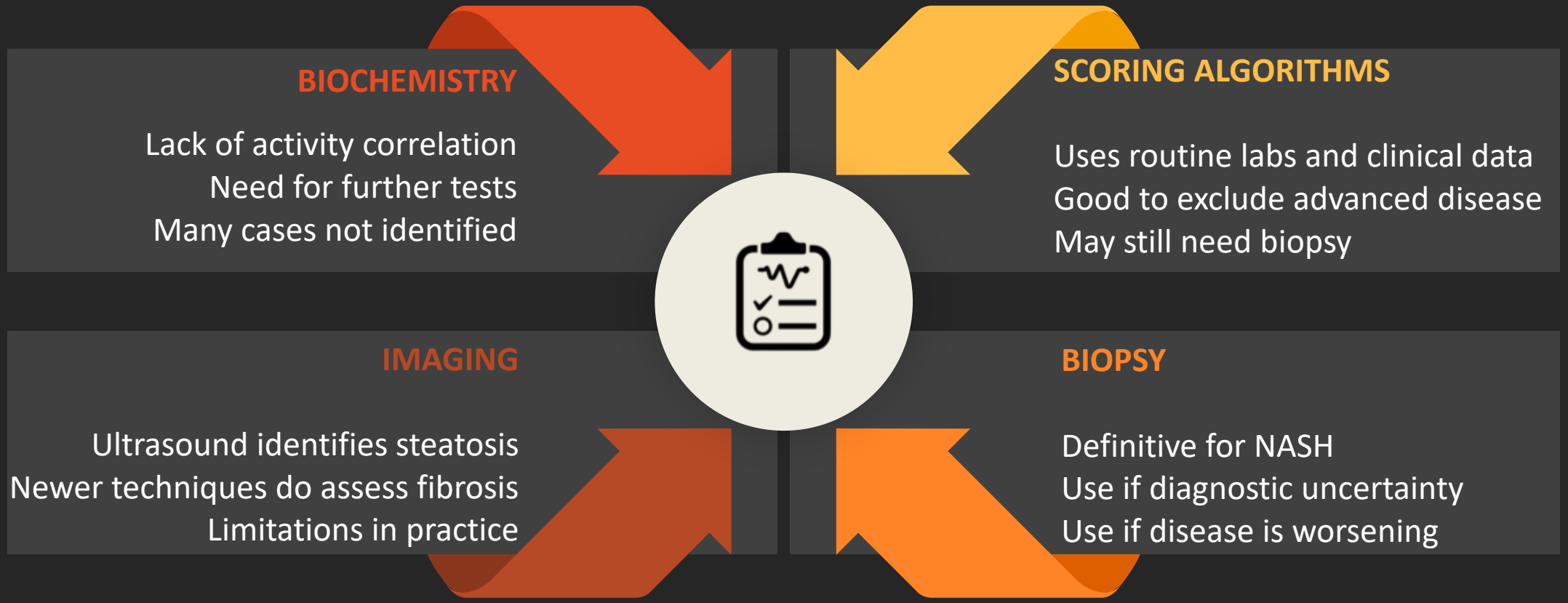
Imaging is imperfect

Predictive Scores' NPV better than PPV

Biopsy remains definitive for NASH

- No single non-invasive test is ideal
- Many patients ultimately require biopsy anyway

Methods for investigating non-alcoholic fatty liver disease



Non-invasive scores for fibrosis prediction

Score	Indices	Calculation	Interpretation
BARD score	BMI AST/ALT ratio T2DM	Weighted sum: 1. BMI ≥28=1 point 2. AAR ≥0.8=2 points 3. T2DM=1 point	Validated in 827 patients with biopsy proven NAFLD fibrosis Score ≥2: Se 0.91, Sp 0.66, NPV 0.96 AUROC 0.81 for stage 3–4 fibrosis
NAFLD fibrosis score	Age Hyperglycaemia BMI Platelet count Albumin AST/ALT ratio	−1.675+0.037×age (years)+0.094×BMI (kg/m^2) +1.13×IFG or diabetes (yes=1, no=0) +0.99×AST/ALT ratio—0.013×platelet (×109/L) —0.66×albumin (g/dL)	Validated in 733 patients with NAFLD AUROC 0.88 for stage 3–4 fibrosis
FIB-4 score	Age AST ALT	Age×AST (IU/L)/platelet count (×109/L)×$\sqrt{}$ALT (IU/L)	Validated in 541 patients with biopsy-proven NAFLD AUROC 0.80 for stage 3–4 fibrosis

AAR, AST/ALT ratio; AUROC, area under receiver operating characteristic; BMI, body mass index; IFG, impaired fasting glucose; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; Se, sensitivity; Sp, specificity; T2DM, type 2 diabetes mellitus.

Management Approaches

Patients with NASH have an increased risk of both adverse cardiac and liver outcomes due to their common metabolic risk factors. Management therefore depends largely on disease severity and risk stratification.

Four main areas of focus: lifestyle modification, targeting components of metabolic syndrome, liver-directed pharmacotherapy for high-risk patients, and managing complications of cirrhosis.

Summary of NAFLD management strategies

Diet

- (Reduces steatosis and NASH)
- caloric restriction & weight loss
- further weight loss reduces fibrosis

Exercise

- (Reduces steatosis, LFTs)
- 150-200 minutes per week
- All types effective

Gastric bypass

- (Reduces lipids, NASH, and fibrosis)
- BMI > 50, less or if MetS

Orlistat

- (Reduces ALT, steatosis)
- Combine with lifestyle

Vitamin E

- (Reduces NASH)
- For advanced disease + treatment failure

Pioglitazone

- (Reduces NASH, fibrosis)
- For advanced disease + treatment failure

Dietary Intervention for NAFLD

Calorie Restriction

Approx 600 kcal/day less than required to maintain present weight

Fast Food Avoidance

Avoid saturated fats, simple carbohydrates, sweetened drinks, fructose sodas

Mediterranean Diet

Common feature is high monounsaturated fat intake +/- unprocessed

Omega-3 Fatty Acids

Experimental and small sample evidence for other supplements

Issues in Liver-directed pharmacotherapy

Biopsy-proven NASH when lifestyle intervention has failed

- Pioglitazone
  - ✓ Reduction in hepatocellular injury and fibrosis
  - ✓ For use in diabetics
  - ✓ Reduction in death, MI, stroke
  - ✓ Placebo trials and meta-analysis
- Concerns regarding long-term safety
  - ✓ Weight gain
  - ✓ Reduced bone density
  - ✓ Congestive heart failure
  - ✓ Bladder cancer
- Therefore, proper patient selection, consideration of individual risk profile, and prior evaluation are all valuable
  - ✓ Optimal dose and duration of treatment unknown
- Vitamin E
  - ✓ Beneficial effects on histology in non-DM NASH
  - ✓ Not evaluated in cirrhosis (and some evidence in DM)
- Concerns regarding long-term safety
  - ✓ Possible increase in mortality with higher doses
  - ✓ Hemorrhagic stroke
  - ✓ Prostate cancer
- Reserve for patients with pre-cirrhotic NASH who have failed lifestyle interventions
  - ✓ Optimal dose and duration of treatment unknown

Targeting components of the metabolic syndrome

Diabetes

Screen and treat; DM worsens NASH

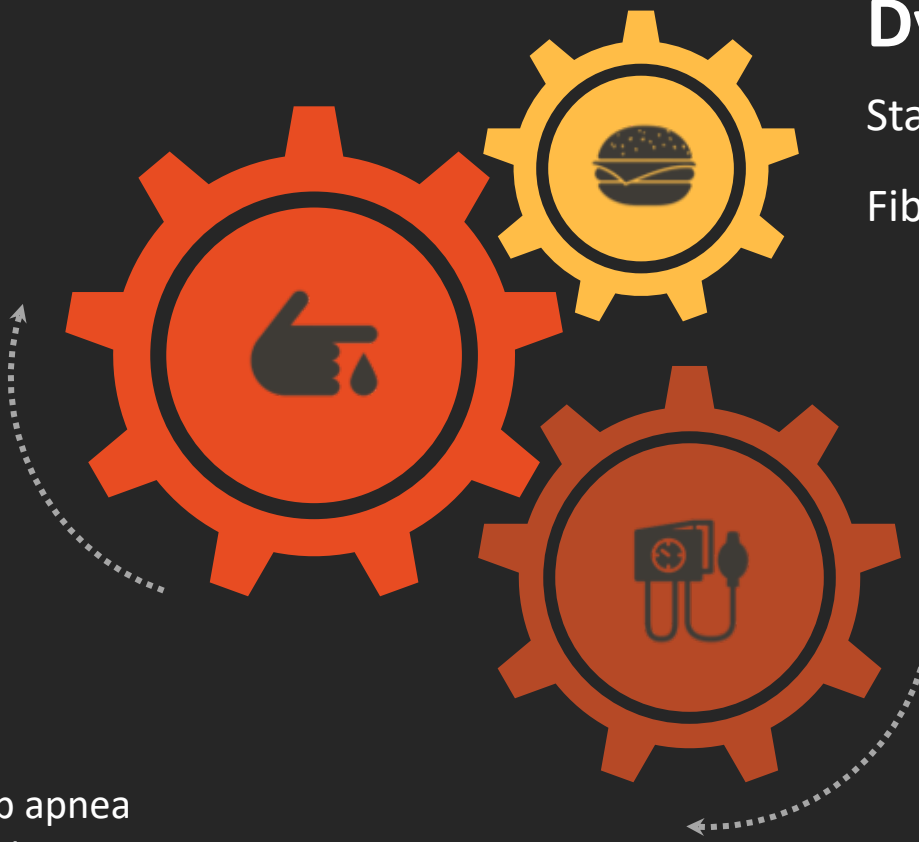
Metformin: wt loss, dec HCC risk

GLP-1 analogues: wt loss, enzymes, steatosis, histology (liraglutide)

Pioglitazone: as discussed

DPP-4i: enzymes and steatosis

SGLT-2: enzymes +/- inflammation



Dyslipidemia

Statins: enzymes, steatosis

Fibrates: inflammation +/- steatosis

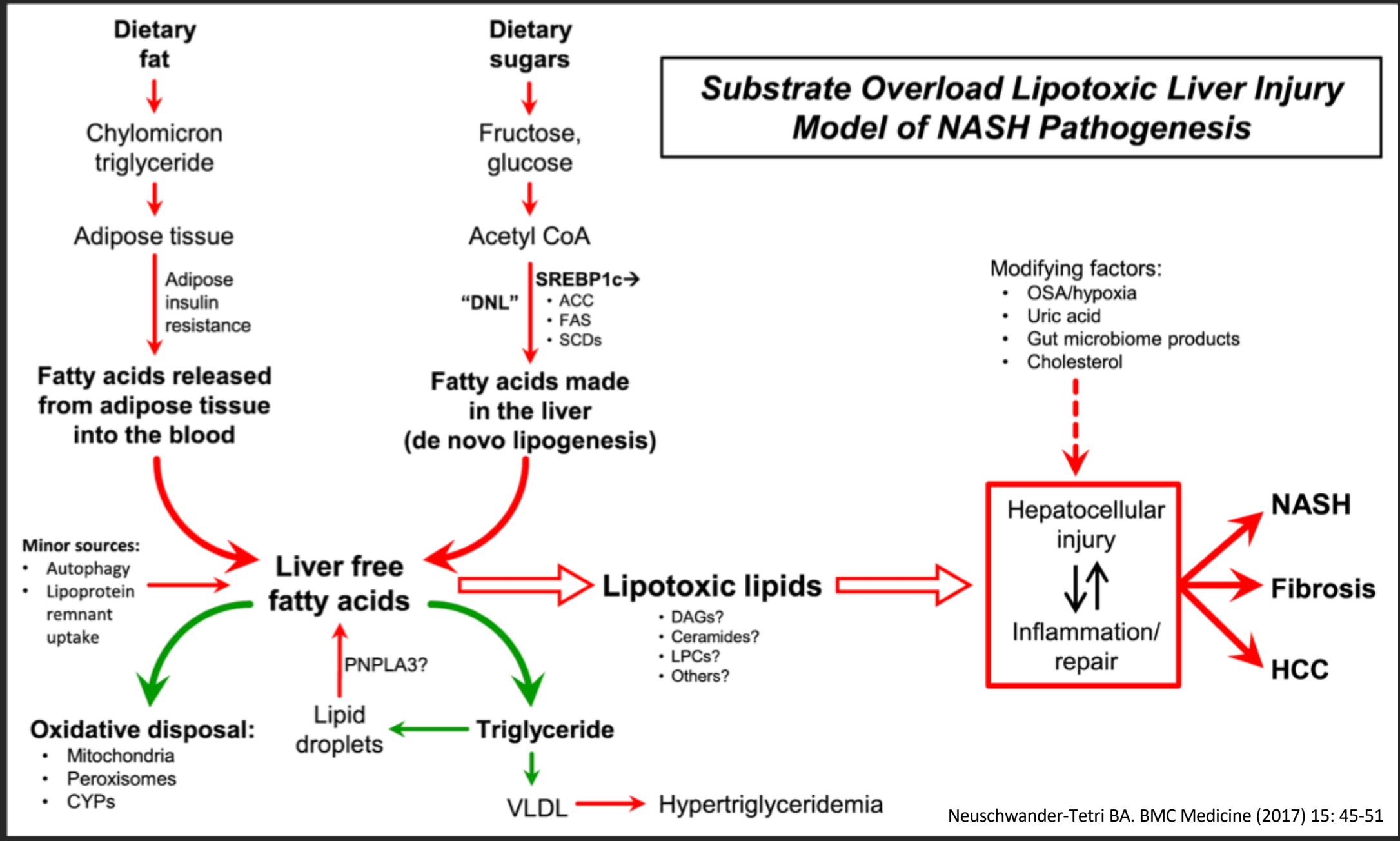
Hypertension

Blocking RAS reduces fibrosis

Possible add-on effects of some ARBs

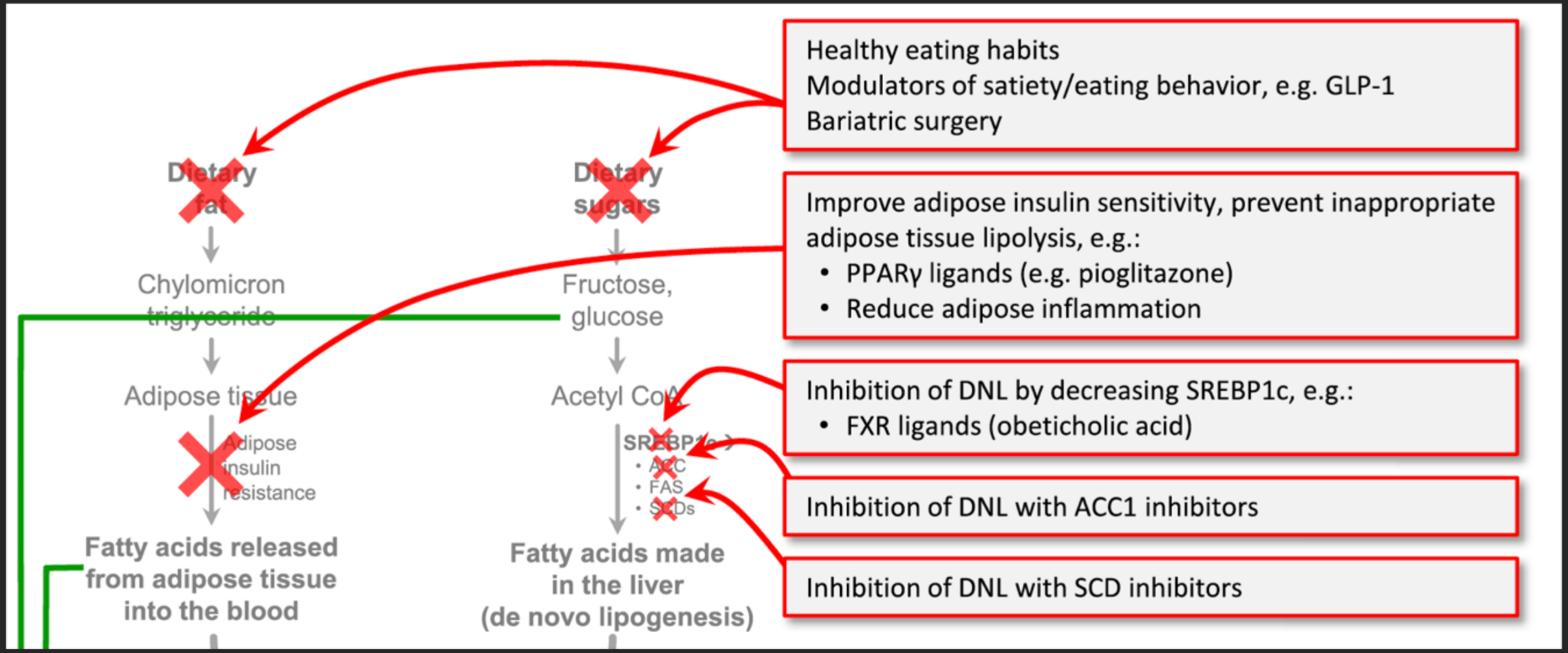
No specific rec's for NAFLD popl'n

Suspect obstructive sleep apnea
Higher risk for NALFD and NASH
Unknown if treatment has benefit

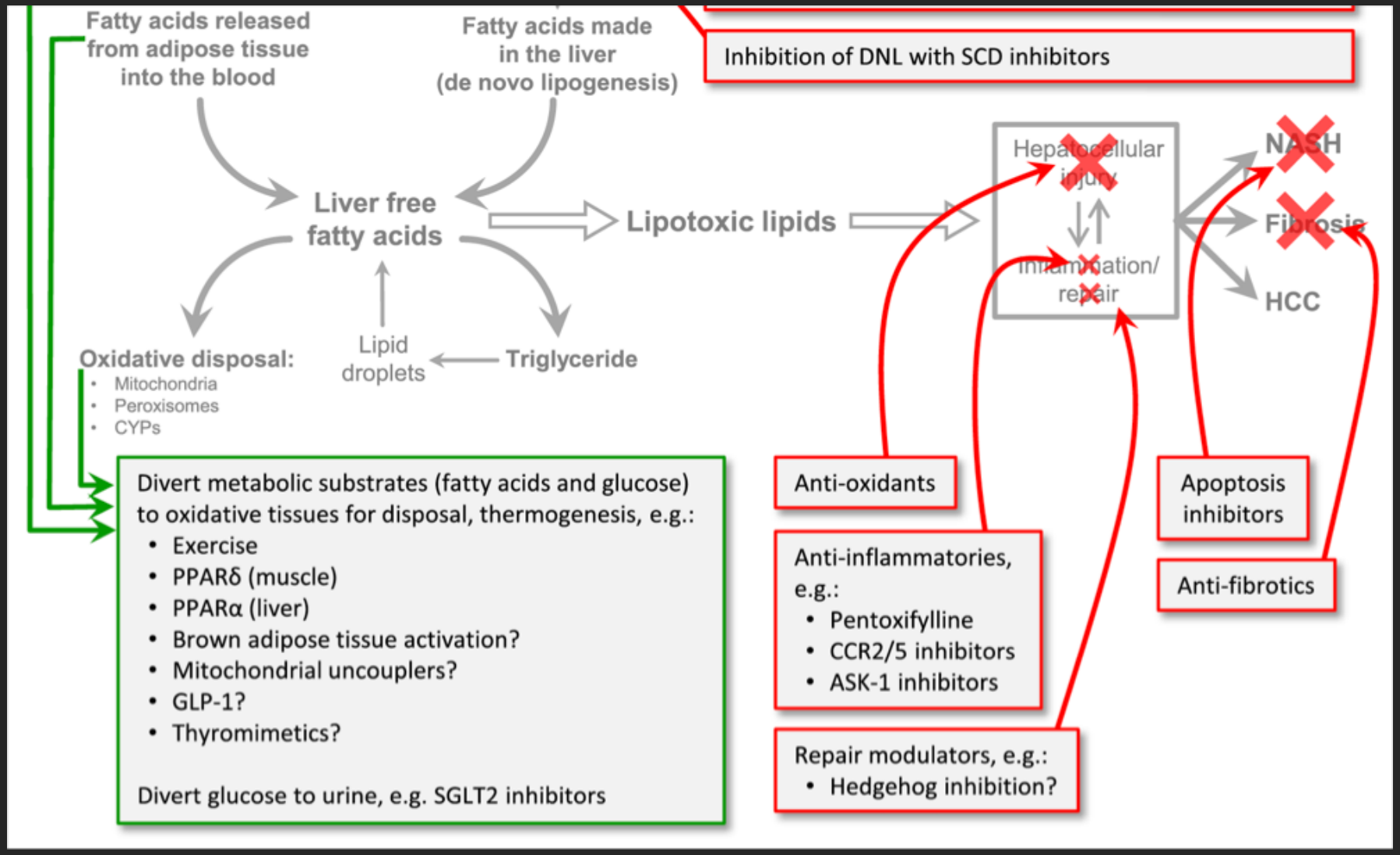


Neuschwander-Tetri BA. BMC Medicine (2017) 15: 45-51

Potential and predicted therapeutic targets



Potential and predicted therapeutic targets



Key Messages

Common

Co-exists with risk factors

You will encounter NAFLD

Relevance

Multi-modal

Prediction and prognostication

May require biopsy

Diagnosis

Energy substrate overload / toxicity

Variable progression to damage

Risk of cirrhosis

Pathophysiology

Non-pharm foundation

Treat co-existing MetS components

Targeted Rx coming

Management

keep in touch

discuss / **collaborate**

Winnipeg: Health Plus Specialists
1071 Autumnwood Drive R2J 1C6
F: (204) 594-2101 // P: (204) 594-2100
jonathan.gabor@gmail.com

Selkirk: Selkirk Medical Centre
353 Eveline Street R1A 1N1
F: (204) 785-7051 // P: (204) 785-7050