

Steatotic Liver Disease

An integrated pathologic framework for alcohol- and metabolism-associated injury

Alcohol-associated injury

Metabolic dysfunction

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

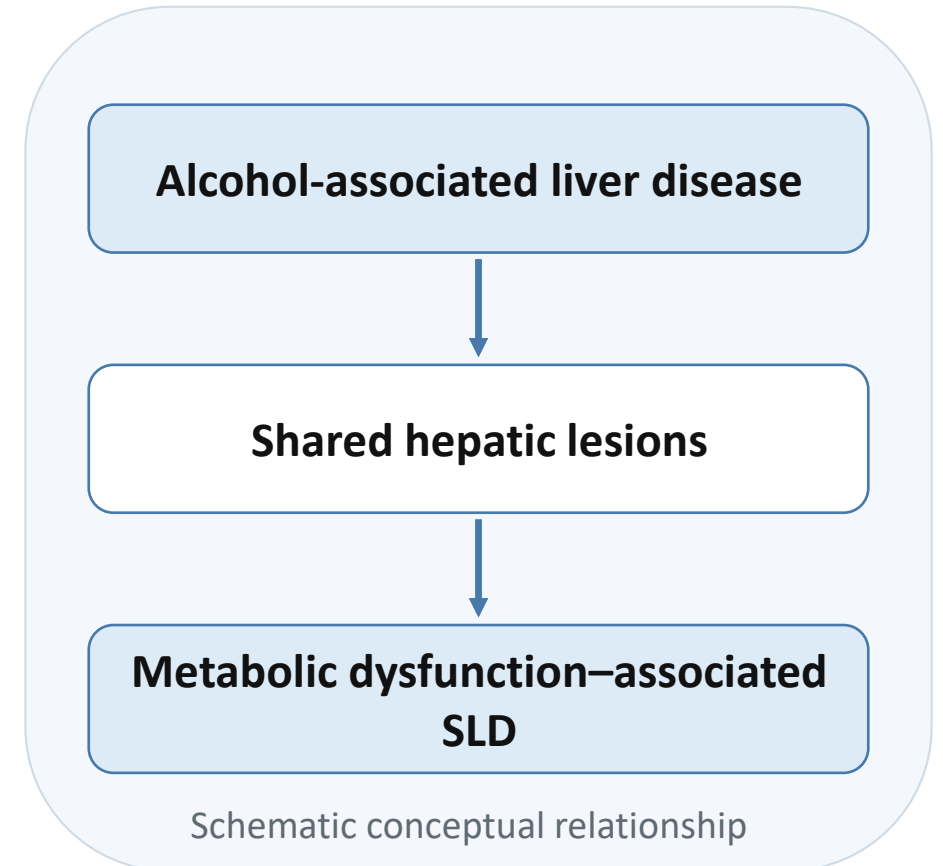
www.abusuraihsakhri.com

Learning objectives

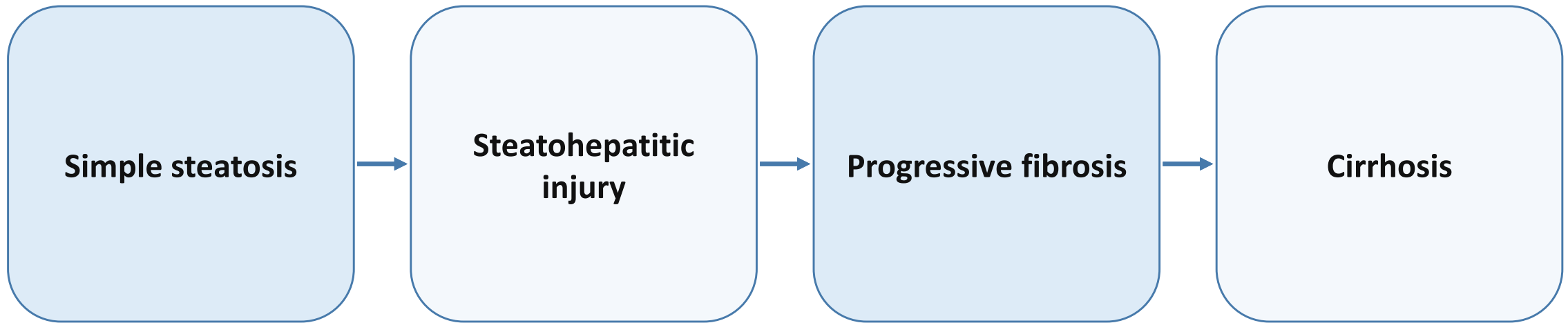
- Distinguish hepatic steatosis, steatohepatitis and progressive fibrosis.
- Explain why alcohol exposure and insulin resistance produce overlapping injury patterns.
- Recognize the key morphologic features and their clinicopathologic significance.
- Explain why etiologic classification requires clinical information in addition to histology.

Steatotic liver disease: An umbrella concept

- The Robbins section groups alcohol-associated liver disease and MASLD because their morphologic patterns overlap.
- The same biopsy patterns can result from different or coexisting etiologic drivers.
- The initiating exposure, systemic context and disease stage are therefore essential for interpretation.



Common morphologic spectrum



- These categories overlap: Fibrosis may coexist with ongoing hepatocellular injury.
- This is a teaching continuum—not a claim that every patient passes through all stages.

Two major etiologic contexts

Alcohol-associated disease

- Ethanol metabolism changes hepatocyte redox balance.
- Acetaldehyde, CYP2E1 induction and gut-derived inflammatory signaling add injury.
- Exposure and host susceptibility influence disease severity.

Metabolic dysfunction–associated disease

- Insulin resistance and dysfunctional adipose tissue increase hepatic lipid burden.
- Oxidative stress and cytokine signaling promote injury and scarring.
- Cardiometabolic comorbidity is central to classification.

Shared injury versus differing initiating factors

Shared microscopic lesions

- Steatosis and ballooned hepatocytes.
- Lobular inflammatory infiltrates and cell death.
- Pericellular/perisinusoidal fibrosis progressing to cirrhosis.

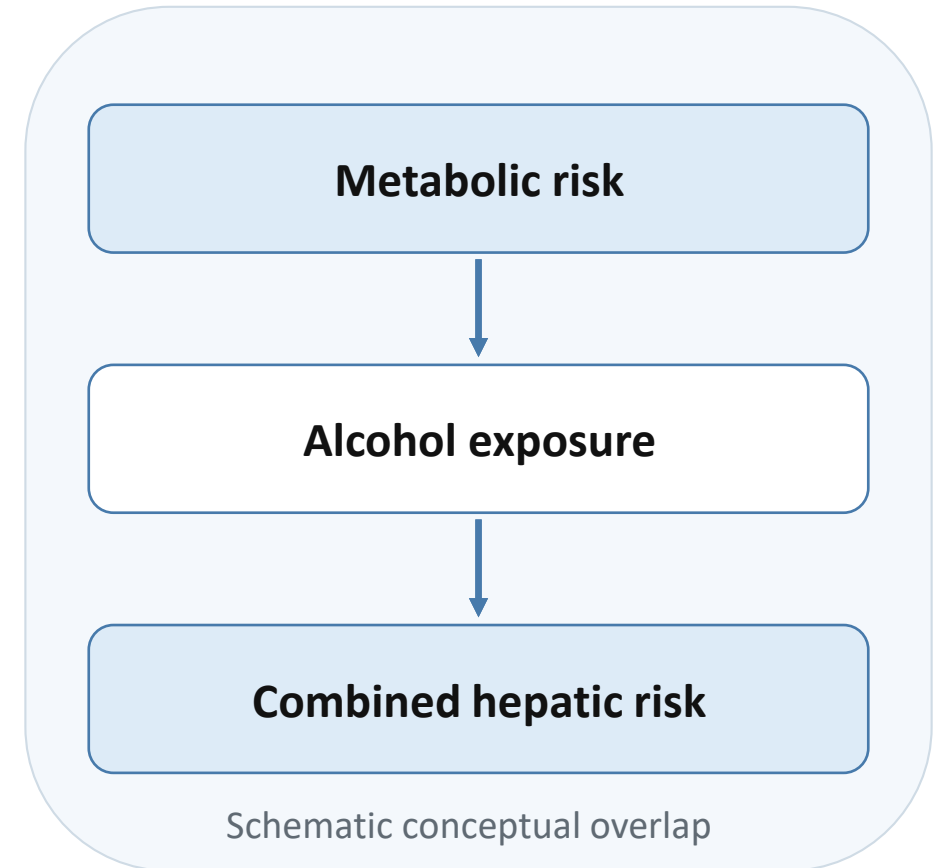
Different clinical evidence

- Pattern and quantity of alcohol consumption.
- Obesity, insulin resistance, diabetes or dyslipidemia.
- Other potential chronic liver diseases and exposures.

Histology describes the injury; History and evaluation identify the likely cause.

Overlap includes combined alcohol and metabolic risk

- Alcohol-related injury and MASLD may coexist rather than being mutually exclusive.
- Robbins recognizes an overlap category termed MetALD for MASLD with increased alcohol intake.
- Concomitant viral infection, iron overload or other liver injury can amplify fibrosis risk.



Why a histologic diagnosis is not enough

- Steatohepatitis is a pattern of hepatocellular injury, not a unique etiologic signature.
- Neutrophils and Mallory hyaline may favor alcohol-associated injury, but are not exclusive.
- An integrated diagnosis combines biopsy findings with alcohol, metabolic and other clinical information.

Do not diagnose alcohol causation solely from a characteristic-looking biopsy.

Acinar zonation helps localize injury

- Zone 3 is the centrilobular/perivenular region of the hepatic acinus.
- Alcohol-associated changes characteristically begin in zone 3 and extend outward.
- Early perisinusoidal fibrosis in steatohepatitis is often centered in this region.



CV = central vein; Alcohol-associated injury begins near zone 3

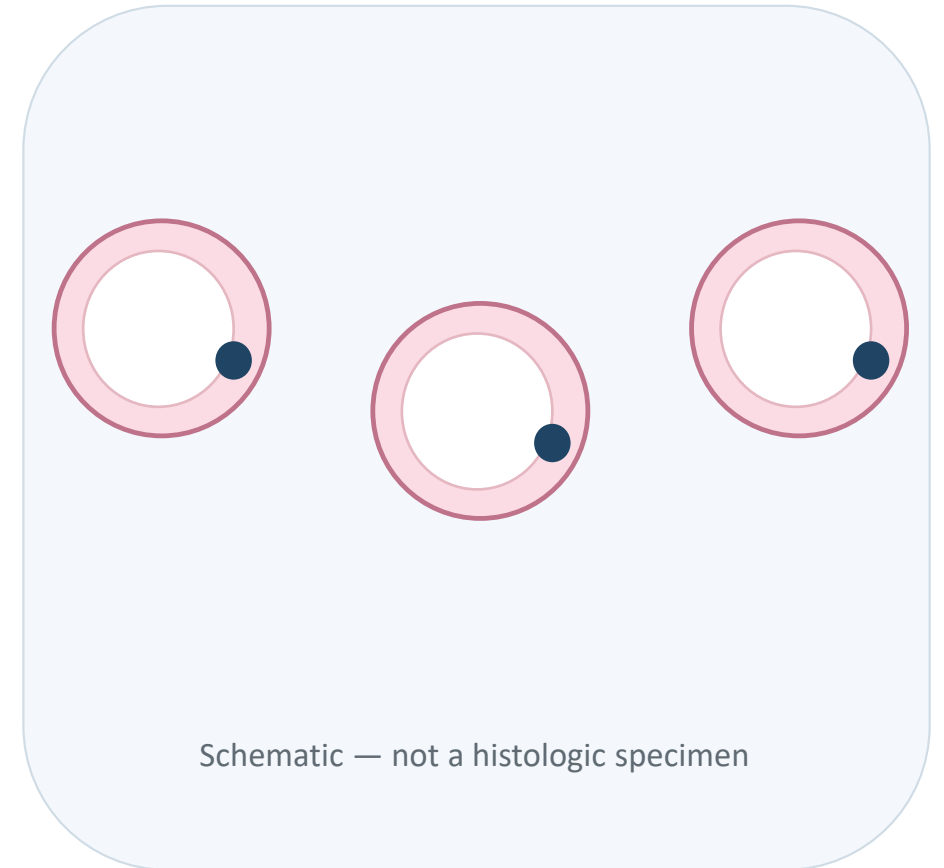
Simplified acinar axis (not a scaled anatomical diagram)

Gross appearance of fatty liver

- With substantial fat accumulation, the liver may be enlarged, soft, yellow and greasy.
- The source describes severe hepatomegaly in long-standing alcohol-associated steatosis.
- Gross appearance indicates steatosis but does not independently identify its cause.

Macrovesicular steatosis: Nuclear displacement

- Large lipid vacuoles expand the cytoplasm and displace the nucleus peripherally.
- Small droplets may merge into one dominant vacuole within a hepatocyte.
- Macrovesicular change predominates in alcohol-associated liver disease.



Macrovesicular and microvesicular patterns

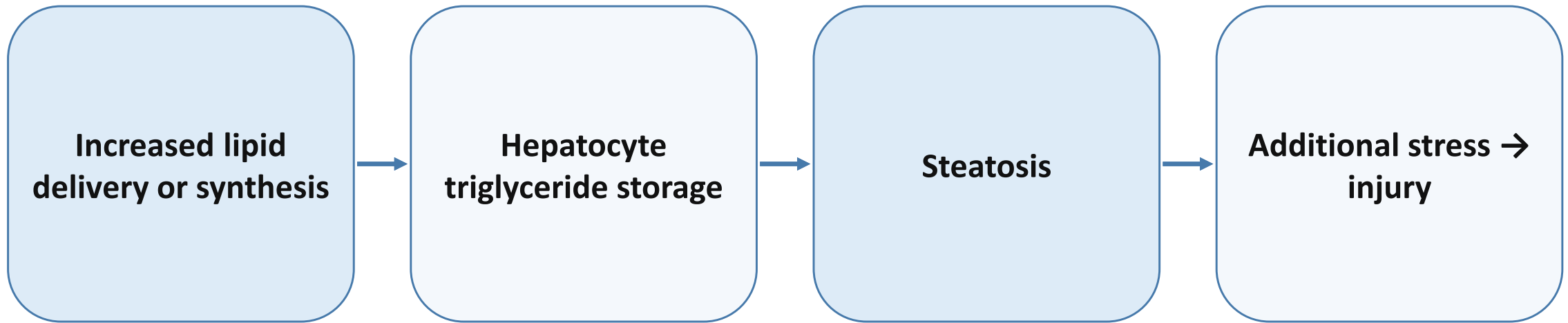
Macrovesicular steatosis

- Large optically empty vacuole; Eccentric, compressed nucleus.
- Common pattern in alcohol-related disease and MASLD.
- Often prominent within a centrilobular distribution.

Small-droplet / microvesicular change

- Many smaller fat droplets may occupy the cytoplasm.
- Alcohol-associated foamy degeneration is a rare exception to the usual macrovesicular pattern.
- Patterns require careful morphologic description.

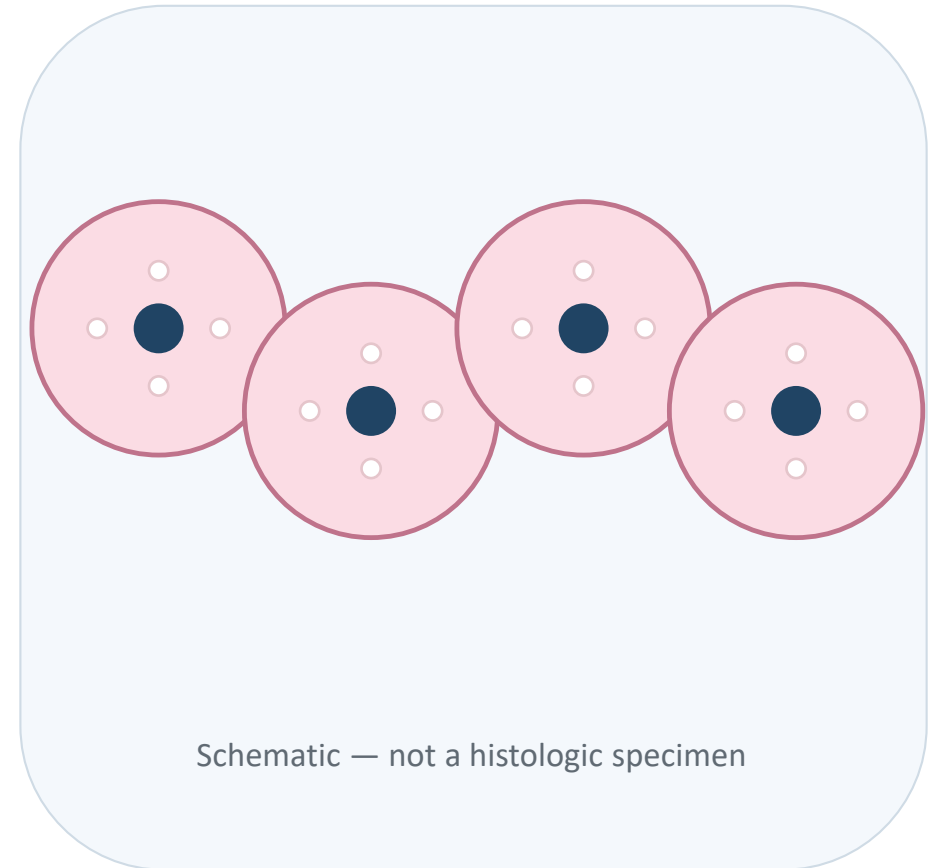
Lipid accumulation can precede cell injury



- Steatosis alone is not synonymous with steatohepatitis.
- In alcohol-associated disease, early fatty change can regress with abstinence.

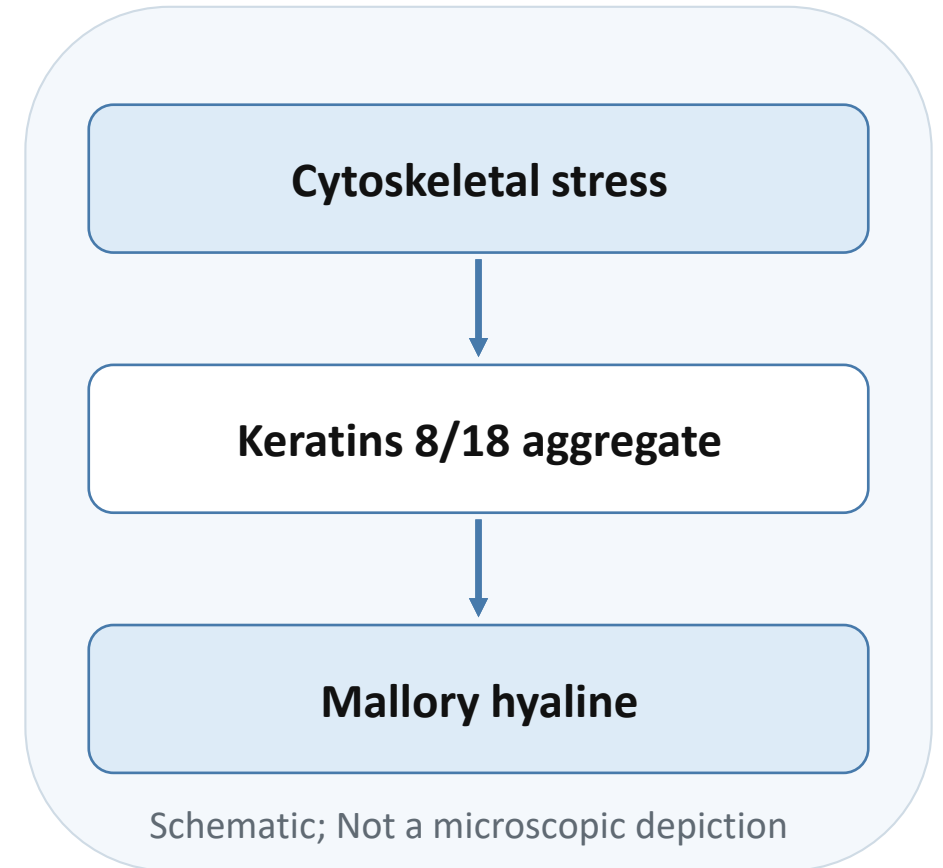
Ballooning signifies hepatocellular injury

- Ballooned hepatocytes are enlarged, with rarefied or cleared cytoplasm.
- The appearance is associated with cytoskeletal disruption and cell injury.
- Ballooning is central to recognizing steatohepatitic injury in both etiologic settings.



Mallory hyaline reflects cytoskeletal injury

- Mallory hyaline consists of aggregated, partially degraded and ubiquitinated cytokeratins.
- Keratins 8 and 18 in these inclusions.
- These inclusions can accompany ballooned hepatocytes but are not specific for alcohol-associated disease.



Inflammation in steatohepatitis

Lobular injury

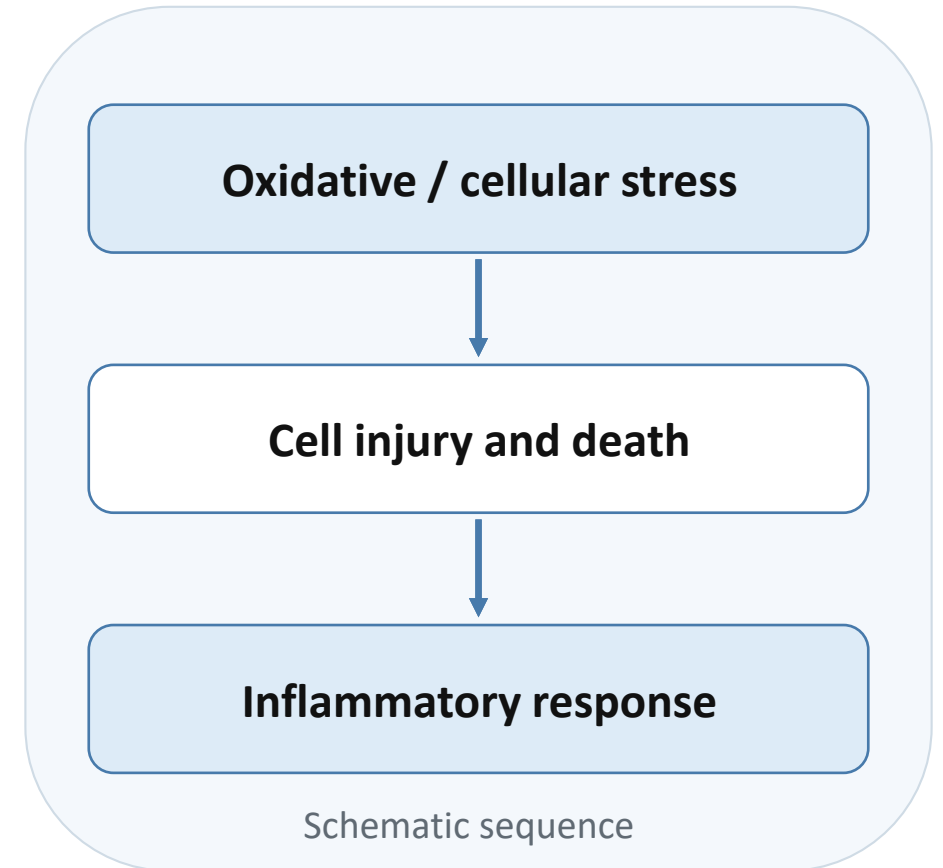
- Lobular inflammatory foci accompany steatosis and ballooning.
- Macrophages and lymphocytes participate in the injury pattern.
- Spotty apoptosis or necrosis may be present.

Alcohol-associated tendency

- Neutrophils are often more conspicuous than in MASH.
- Neutrophils may cluster near ballooned cells with Mallory hyaline.
- The degree of inflammation alone is not a definitive etiologic test.

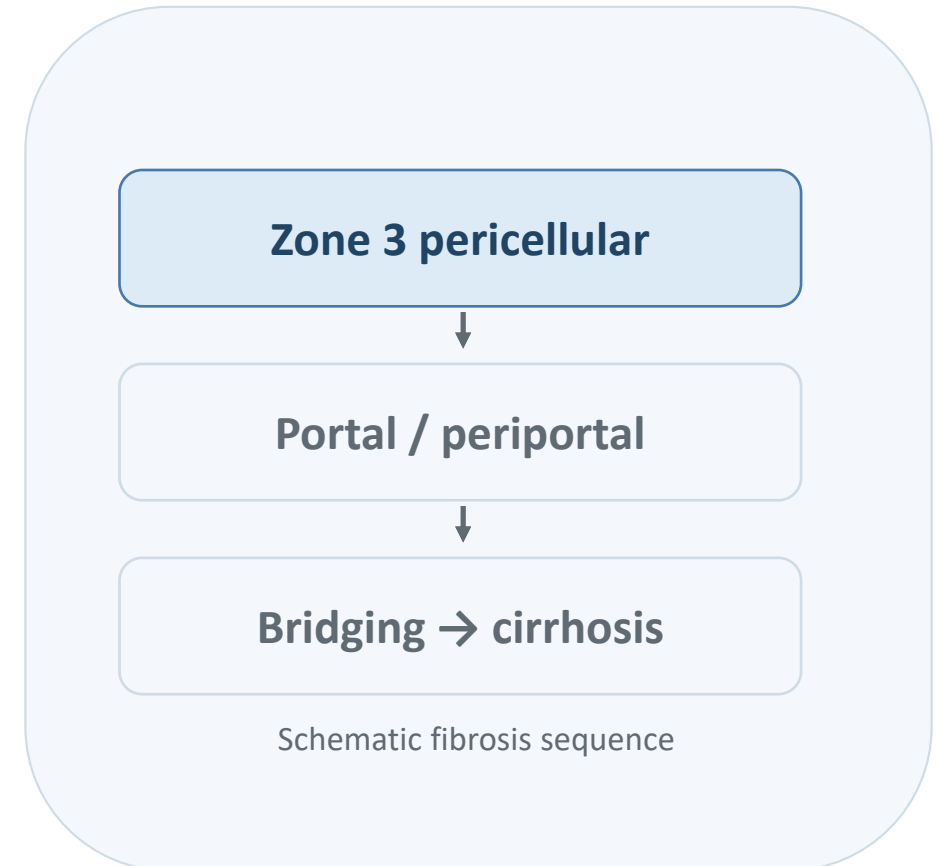
Cell death extends beyond fat storage

- Metabolic and oxidative stresses can damage hepatocyte plasma and mitochondrial membranes.
- Steatohepatitis may show spotty hepatocyte necrosis or apoptosis.
- Progressive injury activates inflammatory and wound-healing responses.

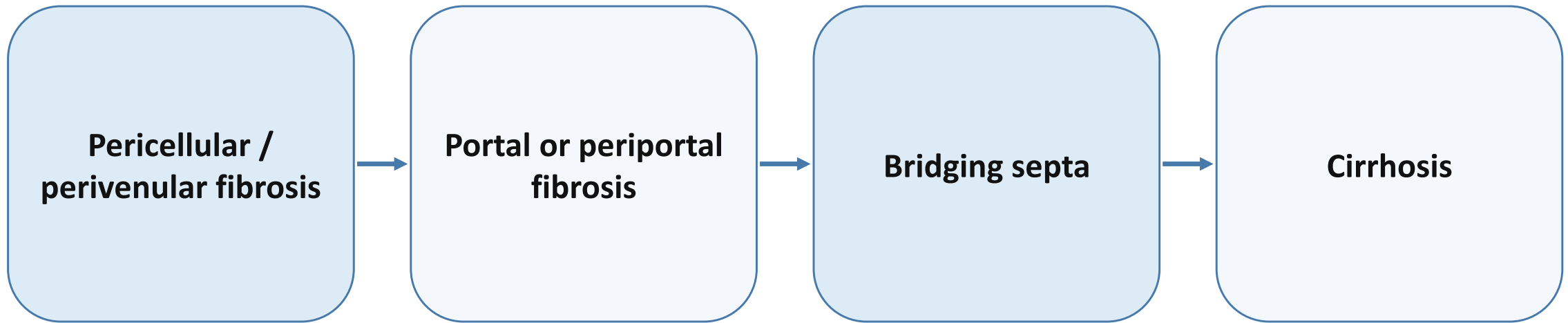


Pericellular fibrosis: “chicken wire” pattern

- Fine perisinusoidal collagen surrounds individual or clustered hepatocytes.
- Early fibrosis is frequently concentrated around zone 3 and central venules.
- A connective-tissue stain such as Masson trichrome can help demonstrate delicate fibrosis.



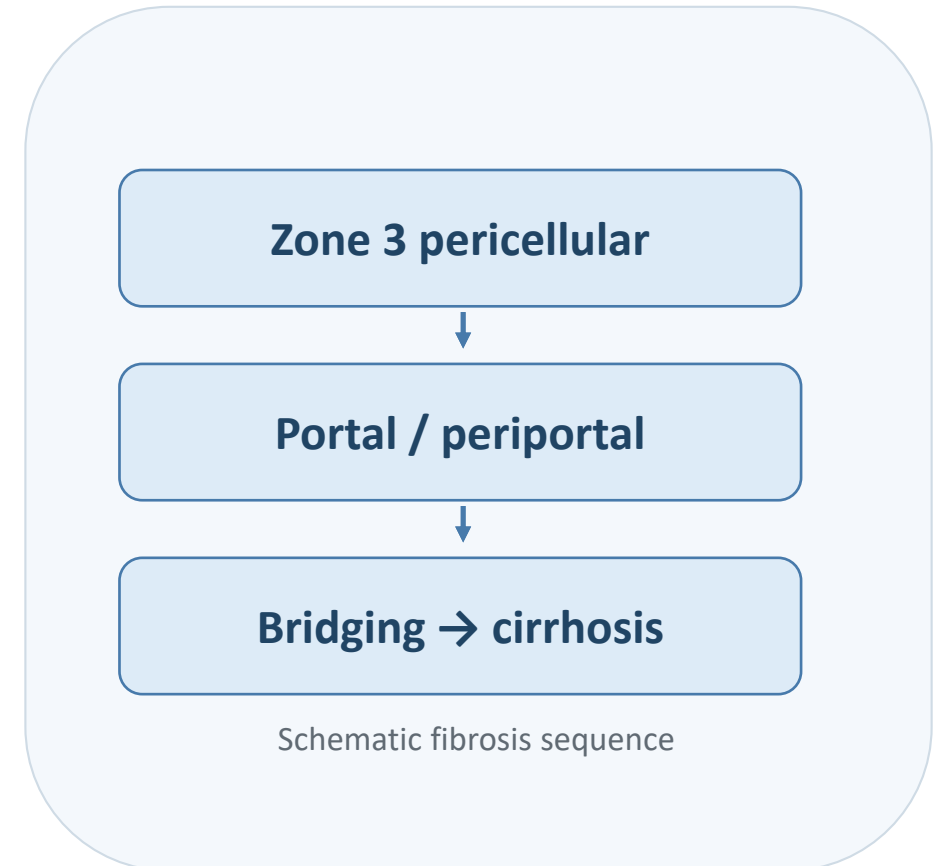
Fibrosis changes the architecture of the liver



- The sequence summarizes typical progression described for steatohepatitis.
- Established cirrhosis includes nodularity and deranged vascular perfusion.

Burned-out disease may lose its fat

- In advanced cirrhosis, visible steatosis and ballooning may be diminished or absent.
- Historical metabolic or alcohol-associated exposure may remain crucial to etiologic attribution.
- Absence of current steatosis does not exclude steatotic disease as the initiating process.



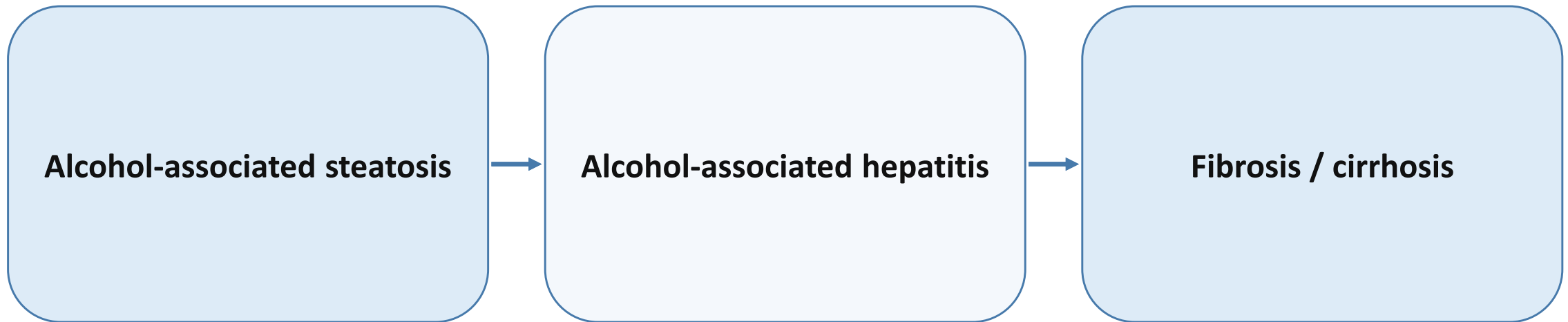
Morphologic findings: What each establishes

Finding	Morphologic significance	Limitation
Steatosis	Hepatic fat storage	Not etiologically specific
Ballooning	Hepatocellular damage	Not exclusive to alcohol or MASH
Lobular inflammation	Active inflammatory injury	Inflammatory intensity overlaps
Pericellular fibrosis	Chronic wound-healing response	Stage, not a unique cause

Interpretation pitfall: Pattern versus diagnosis

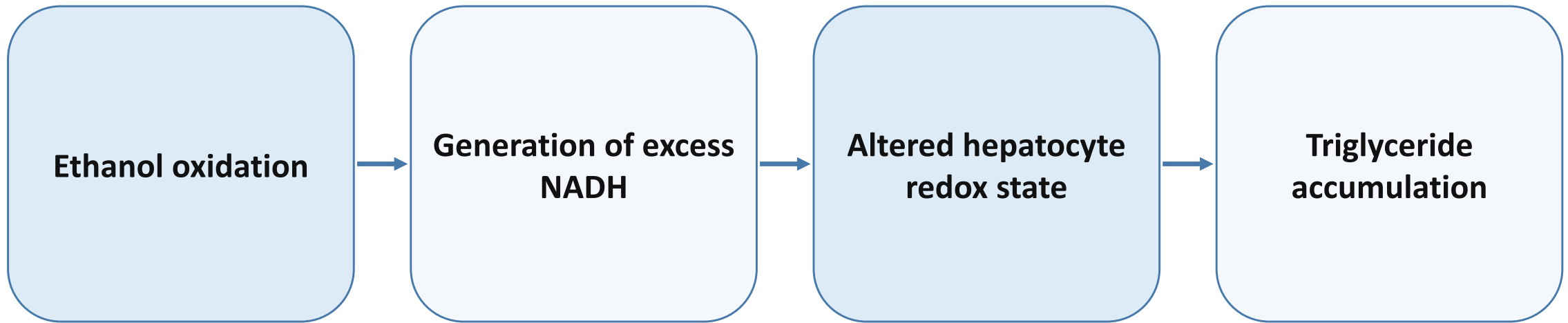
- An observed histologic lesion is not equivalent to a complete clinical disease classification.
- Steatohepatitis can coexist with viral, toxic or inherited liver disease.
- Morphology, exposure history, metabolic profile and exclusion of alternative causes must be integrated.

Alcohol-associated disease comprises overlapping forms



- These lesions can coexist in the same liver.
- Some patients present with cirrhosis without earlier stages being clinically recognized.

Ethanol metabolism shifts hepatic redox balance



- Ethanol metabolism by alcohol and aldehyde dehydrogenases increases NADH production.
- The resulting metabolic imbalance favors lipid retention.

How altered redox balance promotes steatosis

Less lipid disposal

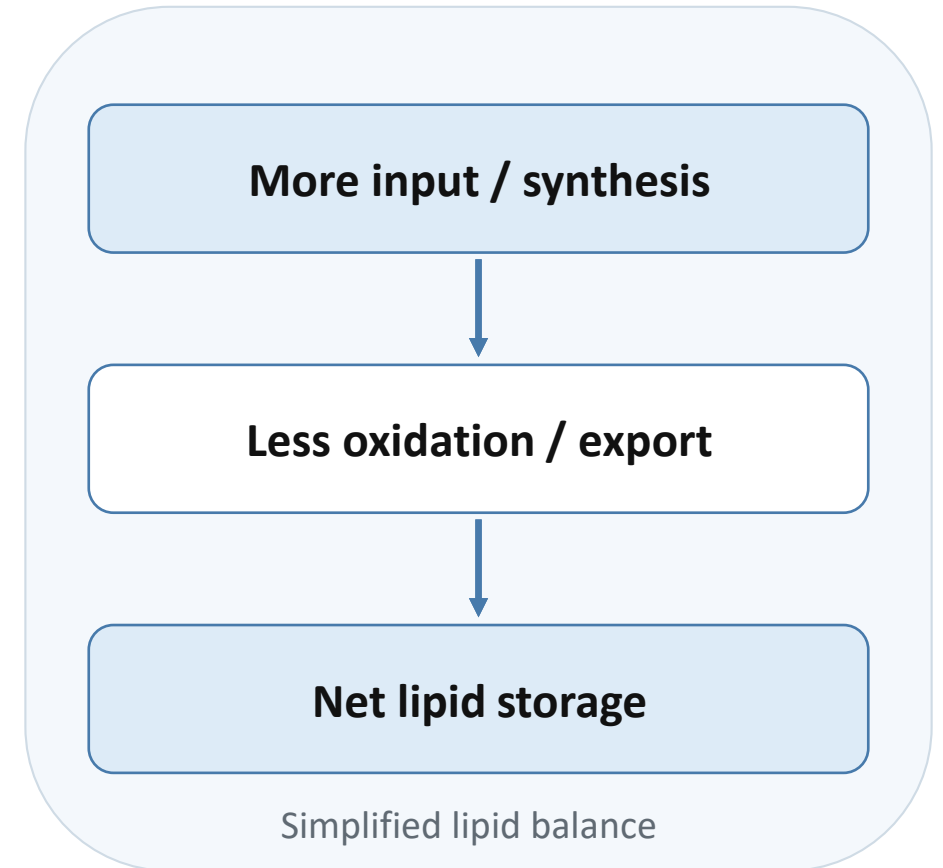
- Raised NADH suppresses fatty acid oxidation.
- Reduced oxidative disposal leaves more substrate for storage.
- Triglycerides accumulate in hepatocyte vacuoles.

More hepatic lipogenesis

- Alcohol increases expression of lipogenic enzymes.
- Peripheral lipid mobilization can increase hepatic lipid supply.
- Impaired lipoprotein secretion may amplify retention.

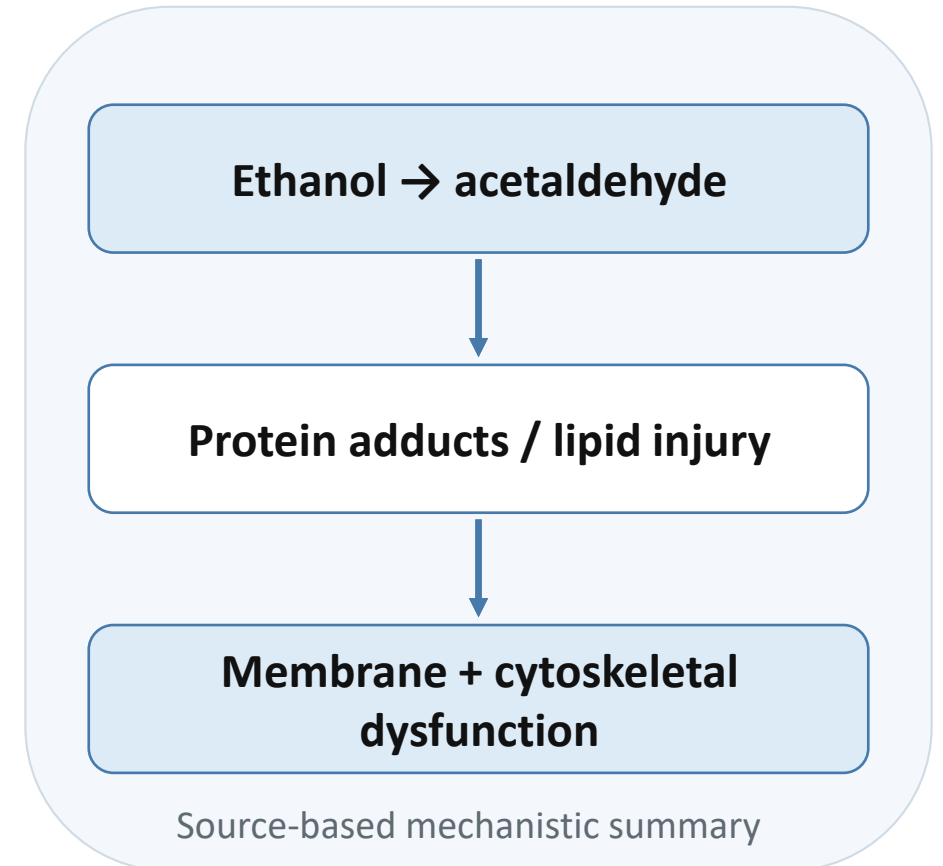
Lipoprotein export is another point of failure

- The amount of hepatic lipid depends on input, synthesis, oxidation and export.
- Alcohol may impair assembly and secretion of lipoproteins.
- This effect can act together with increased synthesis and reduced oxidation to cause steatosis.

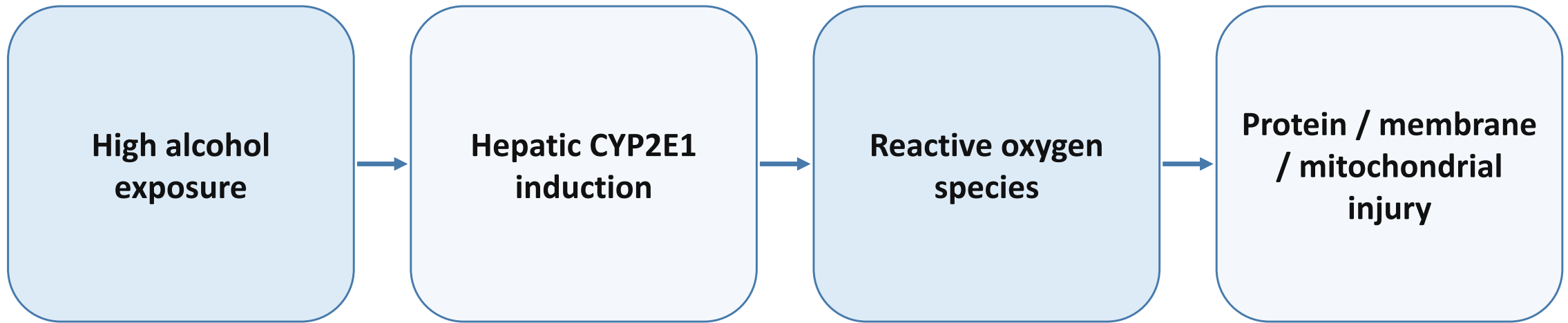


Acetaldehyde causes more than metabolic change

- Acetaldehyde is a reactive product of ethanol metabolism.
- It promotes lipid peroxidation and acetaldehyde–protein adduct formation.
- Cytoskeletal, membrane and potentially immune-mediated effects add to hepatocellular injury.



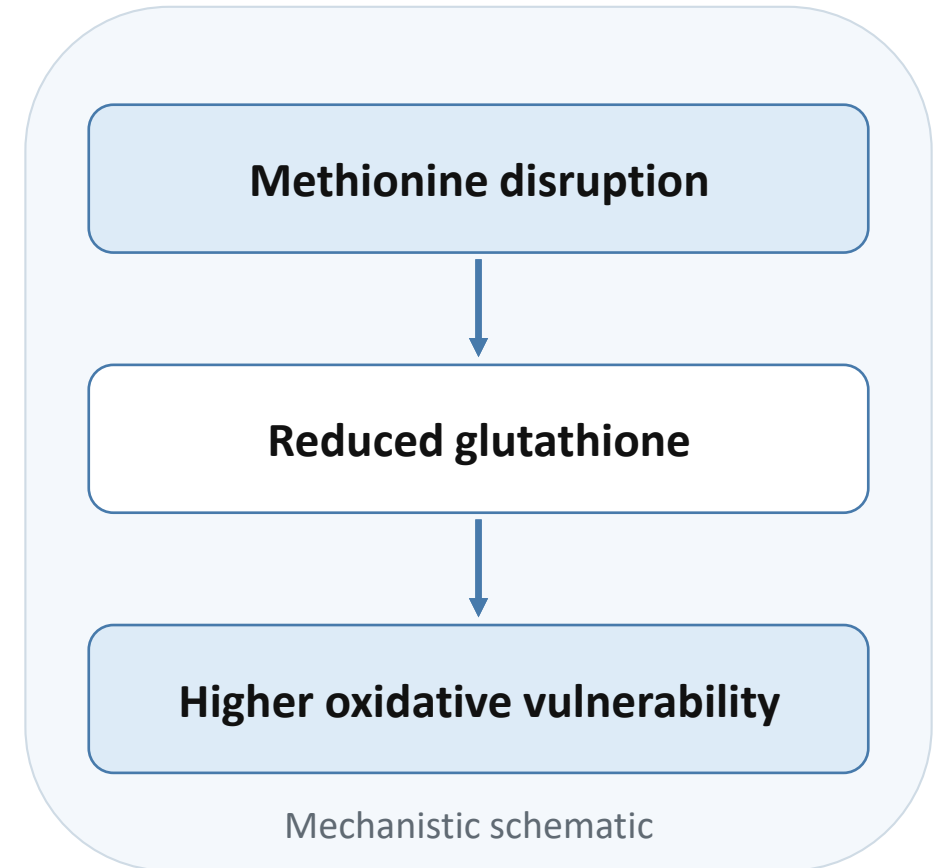
CYP2E1 links ethanol exposure to oxidative stress



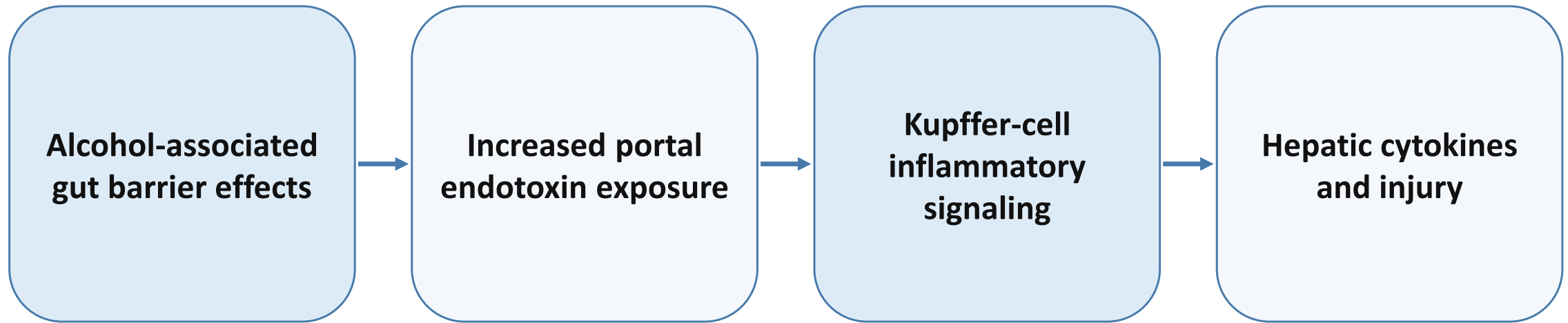
- CYP2E1 is a microsomal cytochrome P450 enzyme.
- Oxidative injury can promote hepatocyte apoptosis.

Reduced antioxidant defense worsens injury

- Alcohol disrupts hepatic methionine metabolism.
- Lower glutathione availability sensitizes the liver to oxidative damage.
- Altered homocysteine metabolism may contribute to endoplasmic reticulum stress.



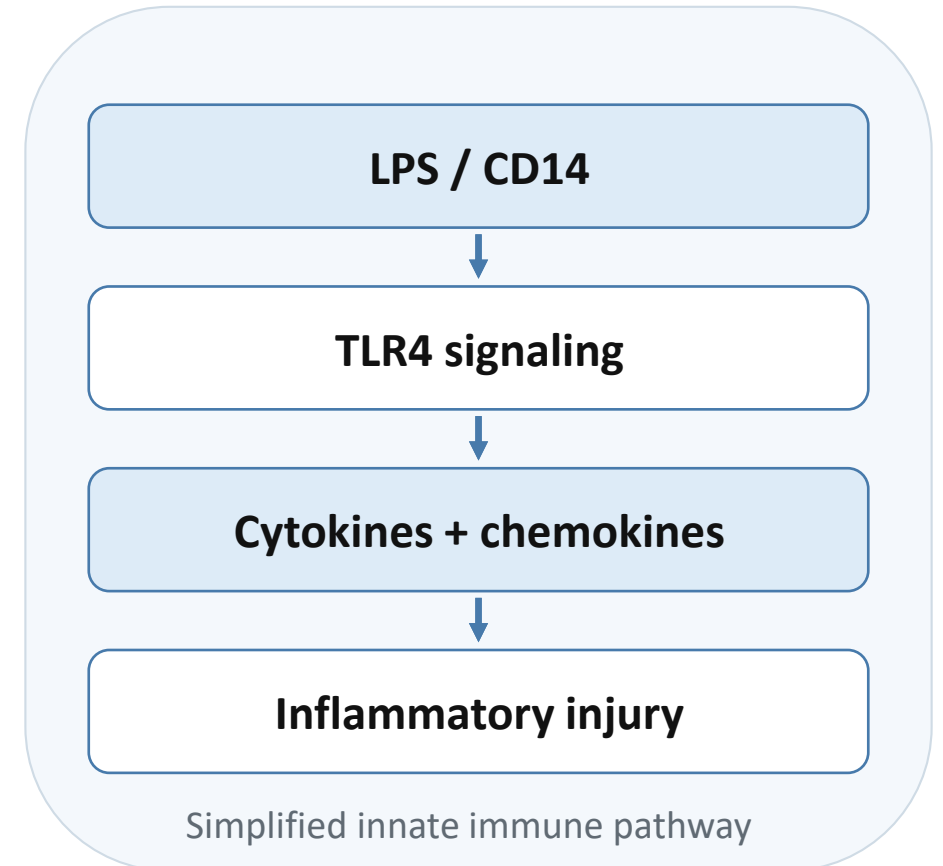
Alcohol-associated disease engages the gut–liver axis



- Gut-derived lipopolysaccharide and innate immune activation.
- The contribution is biologically plausible but individual causal pathways remain complex.

CD14–TLR4 signaling contributes to inflammation

- Gut-derived LPS can interact with CD14 on hepatic Kupffer cells.
- TLR4 activation drives inflammatory cytokine and chemokine release.
- DAMPs from dying hepatocytes can further activate innate immune pathways.



Alcohol injury varies among exposed individuals

Host susceptibility

- Risk is not determined by alcohol dose alone.
- Sex-related sensitivity is described.
- Genetic variants in alcohol metabolism and immune responses may modify injury.

Concurrent hepatic insults

- Chronic viral hepatitis or iron overload can amplify damage.
- Metabolic steatohepatitis can overlap with alcohol injury.
- A multifactorial evaluation is needed for mixed exposures.

Genetic variation may influence alcohol responses

- Twin data support a genetic contribution to alcohol-associated disease susceptibility.
- Alcohol-metabolizing enzymes differ in activity among individuals.
- Reduced aldehyde dehydrogenase activity in an ALDH2 variant associated with alcohol intolerance.

Alcohol-associated morphology often begins in zone 3

- Early lipid deposition and subsequent fibrosis tend to be prominent in centrilobular regions.
- More severe disease can extend outward toward portal tracts.
- Pattern is suggestive but is not a standalone etiologic diagnostic test.



CV = central vein; Alcohol-associated injury begins near zone 3

Simplified acinar axis (not a scaled anatomical diagram)

Alcohol-associated hepatitis: Histologic pattern

Hepatocellular injury

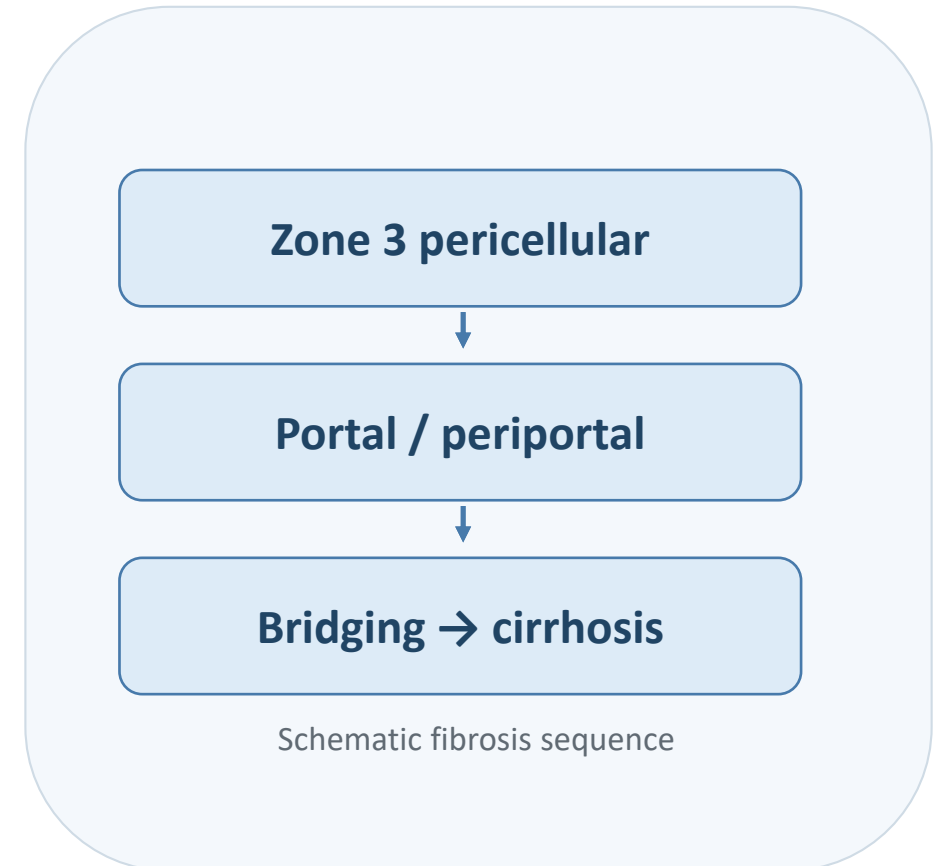
- Ballooned hepatocytes, sometimes with Mallory hyaline.
- Spotty necrosis/apoptosis; More extensive injury in severe cases.
- Mixed steatosis may persist.

Associated response

- Neutrophilic lobular infiltration is often conspicuous.
- Lobular macrophages and lymphocytes contribute.
- Zone 3 pericellular or perivenular fibrosis may accompany injury.

Fibrosis also distorts hepatic microcirculation

- Chronic alcohol-associated damage produces pericellular and perivenular scarring.
- Progressive fibrosis may bridge vascular compartments and form nodules.
- Fibrous obliteration of venous structures contributes to abnormal perfusion in established cirrhosis.



Clinical presentation: Alcohol-associated steatosis

- Patients may have hepatomegaly with only mild biochemical abnormalities.
- Severe hepatic dysfunction is unusual when isolated steatosis is present.
- Alcohol cessation and adequate nutrition can reverse early fatty change.

Clinical presentation: Alcohol-associated hepatitis

- An episode may follow heavy drinking and appear as acute systemic illness.
- Symptoms can include malaise, anorexia, weight loss and upper abdominal discomfort.
- Tender hepatomegaly, jaundice and inflammatory blood-test changes may be observed.
- Severe presentations may resemble acute liver failure or cholestatic disease.

Biochemistry can support—but not prove—etiology

Alcohol-associated pattern

- AST is often higher than ALT.
- A ratio around 2:1 or greater may support suspicion when the history is uncertain.
- Hyperbilirubinemia and alkaline phosphatase elevation can accompany active hepatitis.

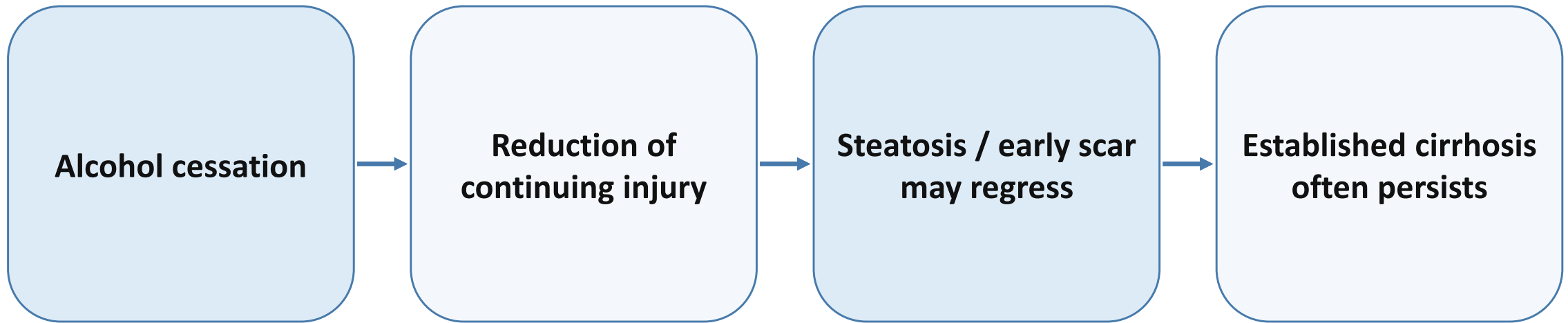
Important interpretive limits

- AST:ALT ratio alone is neither a definitive test nor a histologic classification.
- Severity and clinical context govern interpretation.
- Coexisting liver conditions must remain in the differential.

Cirrhosis is the major advanced consequence

- Regenerative nodules and fibrous septa remodel the liver architecture.
- Portal hypertension and impaired synthetic capacity underlie many complications.
- Liver failure, hemorrhage, infection and hepatocellular carcinoma are recognized late risks.

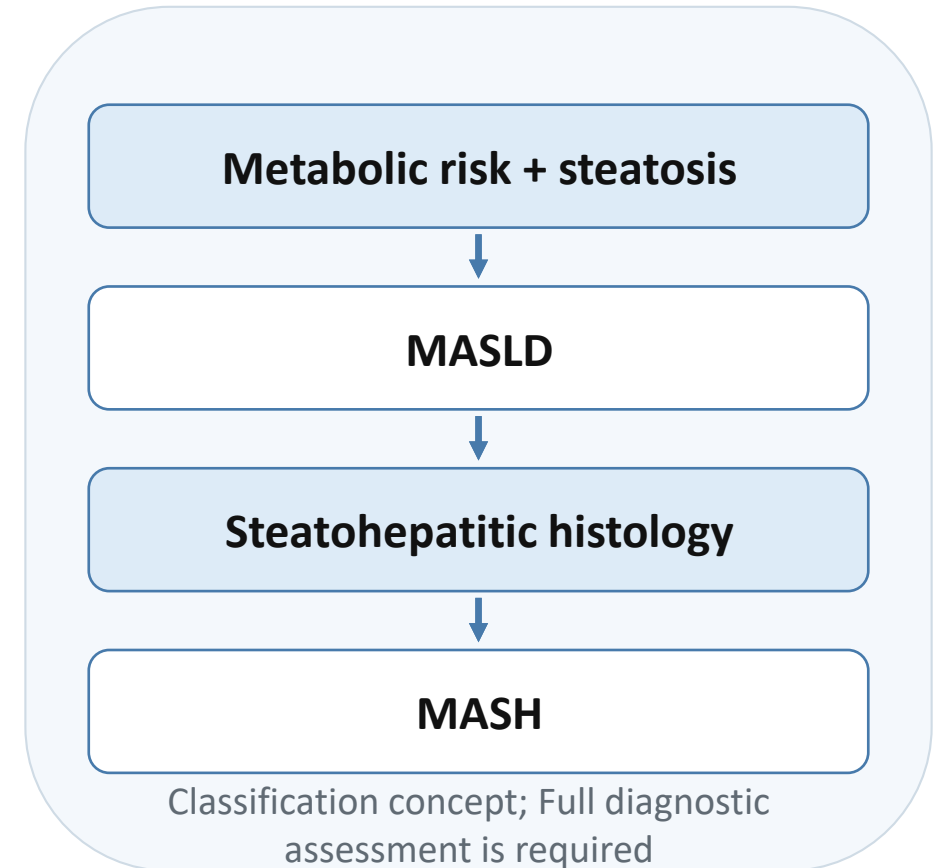
Withdrawal can change the path of alcohol injury



- The reversibility of histologic change depends on stage.
- Complete reversal of alcohol-associated cirrhosis is uncommon in the source text.

MASLD and MASH: Definitions in the source

- MASLD denotes hepatic steatosis associated with cardiometabolic risk, in the absence of another sufficient explanation.
- MASH describes MASLD with steatohepatitic hepatocellular injury.
- The textbook contrasts the newer names with NAFLD and NASH terminology.



Cardiometabolic context is foundational

Commonly associated conditions

- Obesity, particularly increased visceral adipose mass.
- Type 2 diabetes mellitus and insulin resistance.
- Dyslipidemia and metabolic syndrome.

Why context matters

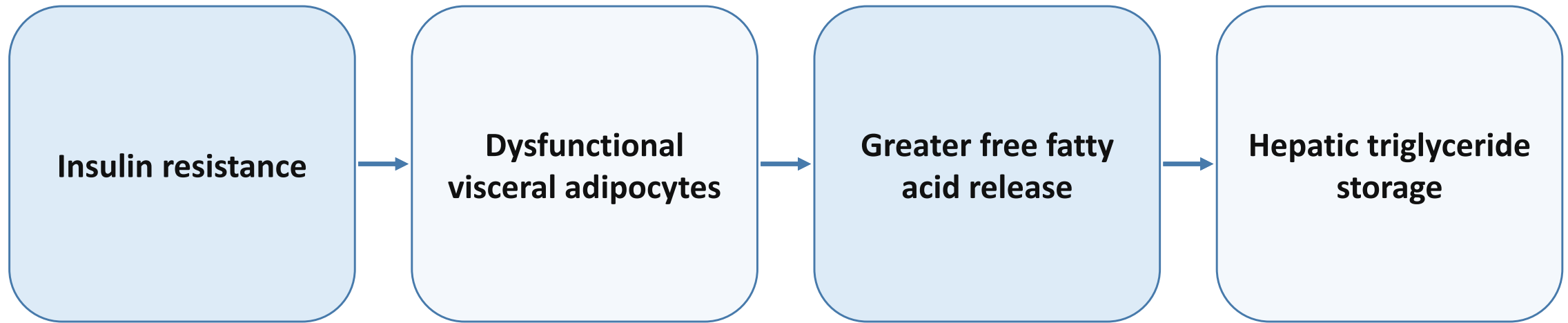
- Metabolic comorbidity raises pretest suspicion.
- It also predicts associated extrahepatic risk.
- The presence of metabolic risk does not automatically exclude an additional hepatic cause.

MASLD requires evaluation beyond steatosis

- The textbook framework includes steatosis and cardiometabolic risk factors.
- History must address alcohol exposure, medications and secondary causes of liver injury.
- Hepatitis C, Wilson disease and other potential etiologies must be considered where relevant.

Do not substitute a fatty liver imaging result for a complete etiologic evaluation.

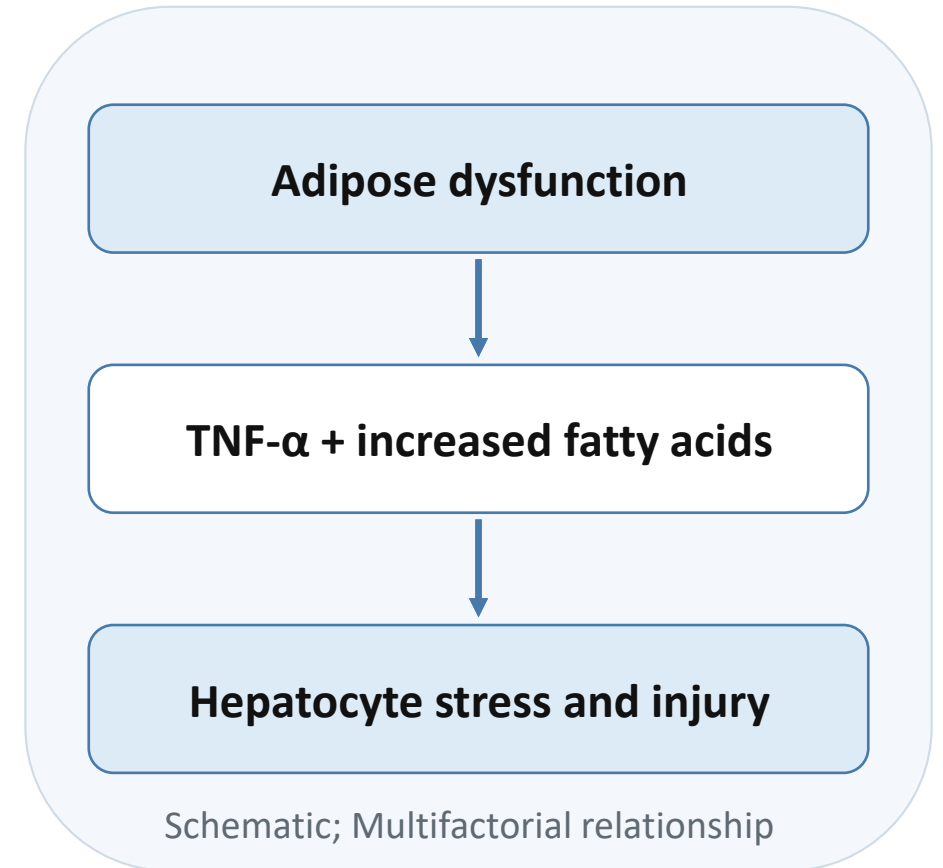
Insulin-resistant adipose tissue increases lipid flux



- The source emphasizes excess free fatty acid delivery to hepatocytes.
- Visceral adipose tissue also produces inflammatory mediators.

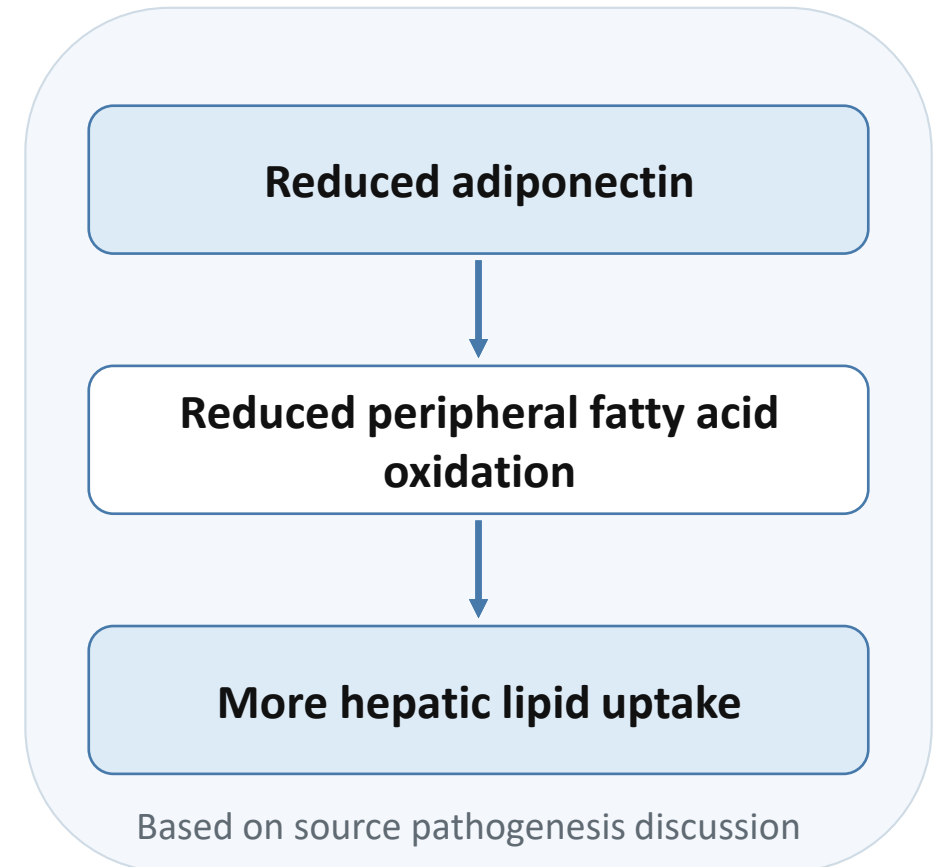
Adipose inflammation contributes to MASH biology

- Dysfunctional adipose tissue releases inflammatory signals, including TNF- α .
- This proinflammatory environment can aggravate hepatocyte stress.
- The degree of steatohepatitis varies despite similar levels of insulin resistance.



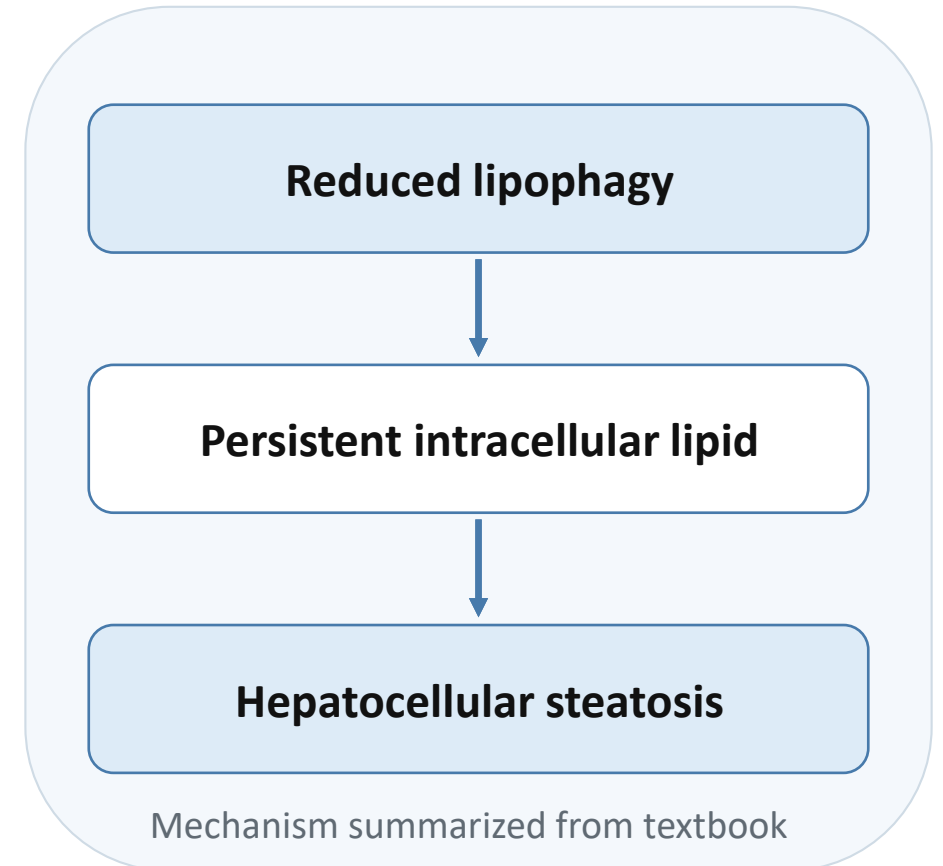
Lower adiponectin reduces lipid disposal

- Insulin-resistant adipose tissue may release less adiponectin.
- This reduces fatty acid oxidation in skeletal muscle and increases the substrate available to the liver.
- The combined effects favor hepatocellular triglyceride accumulation.

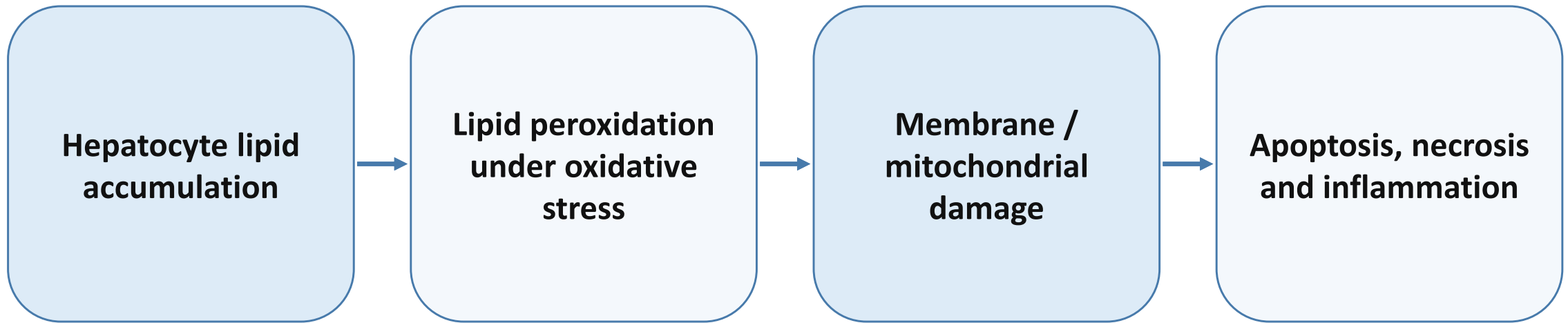


Lipophagy is a second lipid-clearance mechanism

- Lipophagy is selective autophagic turnover of intracellular lipid stores.
- Reduced hepatocyte lipolysis through altered lipophagy in MASLD.
- Decreased lipid clearance can reinforce greater fatty acid delivery and storage.



Oxidative stress links steatosis to injury



- The pathogenesis is multifactorial; Fat accumulation alone does not predict all outcomes.
- Inflammatory responses may amplify damage after the initial insult.

Additional factors linked to MASLD progression

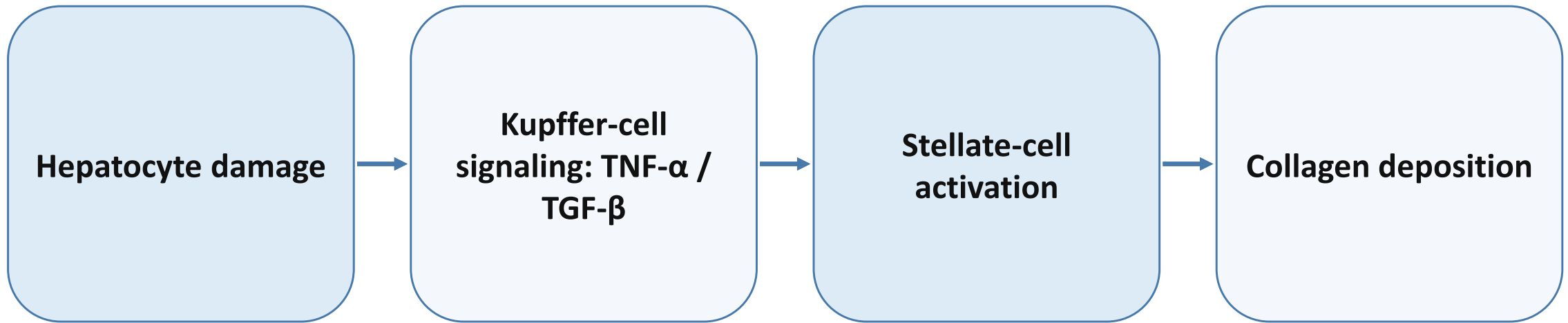
Diet and microbiome

- High-fructose diets are associated with more fibrosis in the source discussion.
- Trans-fat intake may contribute to liver injury.
- Gut-derived endotoxin is associated with inflammatory activation.

Hypoxia and additional liver injury

- Obstructive sleep apnea may contribute via intermittent hypoxia.
- Concurrent hemochromatosis or other chronic injury can accelerate fibrosis.
- These associations do not establish a single causal pathway for every patient.

Cytokines connect hepatocyte injury to fibrosis



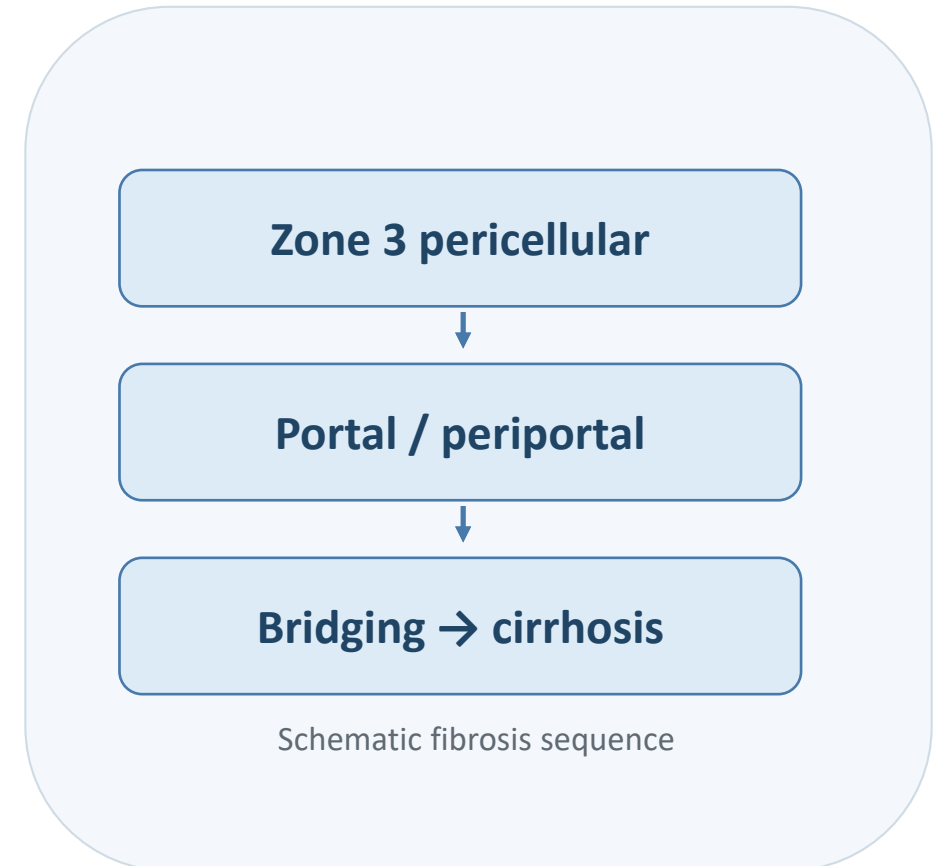
- Persistent wound-healing activity produces pericellular scarring.
- With progression, bridging fibrosis and cirrhosis develop.

Histologic triad of MASH

Component	What the pathologist looks for	Interpretation
Steatosis	Fat in $\geq 5\%$ of hepatocytes	Establishes hepatic steatosis
Ballooning	Enlarged, injured hepatocytes	Required steatohepatitic injury
Lobular inflammation	Inflammatory foci in the lobule	Required component of pattern

MASH fibrosis often begins perisinusoidally

- Zone 3 pericellular collagen deposition may have a fine chicken-wire pattern.
- Trichrome stain can reveal scars that are inconspicuous on routine H&E.
- Later disease often shows periportal fibrosis, bridging and cirrhosis.



Steatohepatitis activity and fibrosis are distinct

Inflammatory activity

- Steatosis, ballooning and lobular inflammatory injury.
- May fluctuate with changing exposures or metabolic control.
- Cannot substitute for an assessment of fibrosis.

Fibrosis burden

- Represents accumulated extracellular matrix and architecture change.
- Advanced fibrosis increases risk of major liver outcomes.
- May persist even when steatosis is less apparent.

Adult and pediatric MASLD differ

Typical adult pattern

- Zone 3 pericellular and perisinusoidal fibrosis is emphasized.
- Steatosis, lobular inflammation and ballooning are central when MASH develops.
- Fibrosis progression may produce bridging septa.

Pediatric pattern

- Steatosis is frequently more diffuse.
- Portal fibrosis may be more prominent than centrilobular fibrosis.
- Ballooning may be absent.

Do not transfer adult histologic expectations uncritically to pediatric liver biopsies.

MASLD can be clinically silent

- Patients with steatosis alone are commonly asymptomatic.
- Liver fat may be detected incidentally on abdominal imaging.
- Some patients with MASH have fatigue or right upper abdominal discomfort with hepatomegaly.
- Biochemical abnormalities may be present despite minimal symptoms.

Imaging and biopsy answer different questions

Imaging / clinical assessment

- Imaging can identify hepatic fat accumulation.
- Metabolic comorbidities and laboratory studies frame the likely disease context.
- Other causes of injury must be considered.

Liver biopsy

- Shows ballooning and lobular inflammation needed for histologic MASH.
- Provides direct assessment of fibrosis.
- Can assist when multiple etiologies are plausible.

A structured differential diagnosis avoids attribution error

- Obtain alcohol history and relevant medication/exposure history.
- Evaluate for viral hepatitis, autoimmune conditions and metabolic or inherited liver disease where indicated.
- Look for possible dual etiologies rather than requiring exactly one cause.
- Interpret fibrosis and inflammation in the complete clinicopathologic context.

Important complications extend beyond the liver

Progressive liver disease

- Advanced fibrosis and decompensated cirrhosis.
- Portal hypertension, hepatic dysfunction and hepatocellular carcinoma.
- In advanced stages, the fatty lesion may be less visible.

Systemic consequences

- Metabolic syndrome often coexists with cardiovascular disease.
- Cardiovascular disease as a frequent cause of death in MASH.
- Overall risk is not captured by liver histology alone.

Alcohol-associated hepatitis versus MASH

Domain	Alcohol-associated pattern	MASH pattern
Driver	Ethanol exposure and susceptibility	Metabolic dysfunction / insulin resistance
Histology	Steatosis, ballooning, inflammation, fibrosis	Same core lesions; overlap substantial
Typical tendency	More neutrophils / Mallory hyaline on average	Often relatively more steatosis
Identification	History and clinicopathologic assessment	Metabolic context and etiologic assessment

Histologic overlap is a deliberate diagnostic warning

- Alcohol-associated steatohepatitis and MASH cannot be reliably distinguished histologically.
- Features reported as more common in alcohol-associated hepatitis are probabilistic tendencies.
- Etiologic attribution requires a careful account of exposure, metabolic features and concurrent disorders.

No single pathologic feature is an alcohol-specific biomarker.

Case application: Acute hepatitis after heavy drinking

Clinical vignette

A patient develops jaundice, tender hepatomegaly and elevated aminotransferases after a period of heavy alcohol intake.

Interpretation question

Which elements support alcohol-associated hepatitis, and what remains uncertain?

The exposure and clinical syndrome support alcohol-associated injury. The diagnosis still requires evaluation for other causes; Steatohepatic biopsy changes would not prove alcohol as the only etiology.

Case application: Incidental steatosis with diabetes

Clinical vignette

Imaging identifies fatty liver in an asymptomatic patient with type 2 diabetes and increased visceral adiposity.

Interpretation question

Can imaging alone establish MASH or advanced fibrosis?

No. The findings raise suspicion for MASLD, but imaging-detected steatosis does not demonstrate the biopsy-defined inflammatory/ballooning pattern of MASH or provide histologic fibrosis staging.

Dual risk factors change the interpretation

Consider both etiologic drivers

- Relevant alcohol intake and metabolic dysfunction may coexist.
- Some patients have viral hepatitis, iron overload or other simultaneous injury.
- The pathologist should communicate pattern and stage precisely.

Clarify the diagnostic question

- Is steatosis present?
- Is there active steatohepatitis?
- How much fibrosis is present, and what is the likely clinical cause?

Integrated high-yield synthesis

- Steatotic liver disease spans relatively reversible fat storage to inflammatory injury, fibrosis and cirrhosis.
- Alcohol and metabolic dysfunction use different upstream mechanisms but converge on overlapping morphologic lesions.
- Ballooning, lobular inflammation and pericellular fibrosis are central histologic concepts.
- Etiology is assigned clinically; Severity and prognosis depend strongly on fibrosis and complications.

Source and interpretation notes

- Primary source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 18, “Steatotic Liver Disease,” pp. 766–771.
- Comparative content draws from the immediately adjacent “Alcohol-Associated Liver Disease” and “Metabolic Dysfunction–Associated Steatotic Liver Disease” sections.
- All diagrams are original, simplified, editable PowerPoint schematics; they do not depict observed specimens or reproduce the textbook’s figures.
- Source material was available as extracted Markdown. Original chapter PDF and licensed textbook images were not available for figure-level verification.