



# NASH

## A new liver disease epidemic

BY ELDON SHAFFER, MD

In the absence of alcohol abuse, steatosis is called non-alcoholic fatty liver disease (NAFLD). Here, droplets of triglyceride accumulate as large fat globules (macrovesicular hepatic fat). The disease is no longer considered an innocuous entity associated with obesity and diabetes. NAFLD can progress from the mere accumulation of fat to inflammation. The combination of NAFLD and inflammation is referred to as non-alcoholic steatohepatitis (NASH), which can lead to liver cell necrosis, advanced fibrosis and eventually cirrhosis with liver failure. NASH is the crucial middle stage in this progression from fatty liver disease to advanced cirrhosis.

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### Causes

#### Obesity

- a consistent association with NASH, especially if severely overweight
- NASH may also occur in obese children and teens
- excessive intra-abdominal fat associated with the Metabolic Syndrome (insulin resistance)

#### “Second hit” model

- likely from abnormal lipid peroxidation and oxidative stress, leading to the release of inflammatory mediators and cell damage

### Prevalence

- affects about 3.1% of people in the U.S.
- common in obesity
  - about 7.6% of Americans are severely obese
  - affects 20% of obese individuals (BMI = 30 kg/m<sup>2</sup>) and more than one-third of those severely obese (BMI = 35 kg/m<sup>2</sup> with complications of obesity, or BMI = 40 kg/m<sup>2</sup>)
- approximately 0.86-3.05 million adults have NAFLD and about 0.3-1.0 million have NASH

### Signs and symptoms

- there are frequently no symptoms; occasionally only an enlarged, smooth liver
- absence of alcohol abuse (i.e. less than 20 g/day for women or less than 30 g/day for men)
- elevated aspartate aminotransferase (2-3 times the normal, and persists > 3 months)

### Investigations

- rule out hepatitis C and other liver diseases
- ultrasound
  - most common diagnostic imaging modality to detect a fatty liver (appears bright)
  - can't distinguish between fatty liver, NASH and more advanced liver disease
- CT scan, MRI and proton magnetic spectroscopy can also detect fatty liver
  - only a biopsy can definitively differentiate NASH from steatosis

### Pharmacology

- Typically reserved for the severely obese (i.e. BMI > 40 or those with BMI > 35 and associated chronic health conditions); combine with a low-fat diet, exercise and behaviour modification
- **Currently being evaluated**
  - insulin sensitizers (e.g. metformin, thiazolidinediones)
    - have potential to be hepatotoxic; still in trial
  - anorectic medications (e.g. sympathomimetics)
    - generally not approved (except for sibutramine, which blocks norepinephrine and serotonin reuptake, and ephedrine, a sympathomimetic amine)
    - side effects (insomnia, dry mouth, hypertension, potential for abuse). Ephedra, a herbal agent, may cause significant CV effects and is banned in the U.S.
    - absence of long-term benefit — limited studies show only modest effects.
  - inhibitors of pancreatic lipase (e.g. orlistat)
    - efficacy not established
  - antioxidant agents (e.g. vitamin E 400 IU q.d.)
    - directed at the “second hit”
    - no current evidence of any effect on metabolic endpoints
  - ursodeoxycholic acid
    - conflicting results on benefits; need better-designed trials

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### Management

- no proven medical treatment exists
- eliminate secondary causes due to corticosteroids, estrogens, tamoxifen, amiodarone, nifedipine and especially alcohol abuse
- weight reduction: diet, behaviour modification and an exercise program; limited evidence for benefit although even a small weight loss improves insulin resistance and its risk factors (e.g. cardiovascular disease, hypertension and diabetes)

### Surgical treatment

**Bariatric surgery appears effective for NASH in severely obese patients when weight loss is modest and gradual.**

- results in > 61.2% loss of excess weight overall
- has a low mortality rate of 1%; 0.5% for gastric bypass procedures
- Metabolic Syndrome completely resolves in 77% of patients; hypertension in 62%
- reduces fat, inflammation and fibrosis in NASH if weight loss is gradual with restrictive procedures
- clinical complications may reach 10%
- lowers mortality and morbidity; less use of healthcare and improved quality of life

### Types of bariatric surgery

#### Malabsorptive procedures

- rearrange the small bowel to decrease its functional length or the efficiency of intestinal absorption
- ileojejunal bypass, an initial procedure, created more metabolic problems (including NASH) than it solved
- newer malabsorptive surgeries include biliopancreatic diversion and its variant, the duodenal switch, which divert the pancreatic and biliary secretions
- these procedures are quite effective for the extremely obese (BMI > 50)
- patients are prone to malnutrition and metabolic problems

#### Restrictive operations

- create a small gastric pouch and a narrow gastric outlet to decrease food intake through early satiety
- gastroplasty-like vertical gastric stapling restricts storage capacity of the stomach
- laparoscopic adjustable gastric banding allows changes in the size of the stoma (gastric outlet) via a subcutaneous port; weight loss is controlled and fewer metabolic complications result
- Roux-en-Y gastrojejunostomy creates a small proximal gastric pouch that empties into the jejunum, combining a restrictive plus a malabsorptive/dumping syndrome component