Fatty liver

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Fatty liver is the accumulation of lipid within hepatocytes. It is the commonest cause of elevated liver enzymes. Some patients will have excess alcohol intake as the underlying cause but there are a significant and growing number of patients with non-alcohol-related fatty liver. This condition has an association with obesity, type 2 diabetes and hyperlipidaemia. Other rare causes are outlined in Table 1.

Terminology

Fatty liver is a descriptive term but lacks clarity. Non-alcoholic fatty liver disease (NAFL) is perhaps a better term, although more cumbersome, because it does imply a spectrum of disease including:

- fatty liver without inflammation
- fatty liver with inflammation
- fatty liver with significant fibrosis / cirrhosis.

The term non-alcoholic steatohepatitis or NASH is in common usage but strictly this term only represents fatty infiltration with significant inflammation.

What causes fatty liver?

The pathophysiology of NAFLD is believed to involve two steps. The first step is fat accumulation within hepatocytes. The underlying problem is insulin resistance which promotes increased peripheral lipolysis resulting in increased delivery of free fatty acids to the liver. After some metabolism free fatty acids are 'packaged' by the liver as VLDL and secreted by the liver. Triglycerides may accumulate in the liver, producing steatosis, when the liver's ability to make and secrete VLDL is exceeded. Steatosis may actually promote further insulin resistance. Usually this is the only step but about 10–15% will develop oxidative stress which activates an inflammatory response (called steatohepatitis). This inflammatory process, if sustained over a long period of time, can lead to significant fibrosis and cirrhosis. It is likely that most cases of cyptogenic cirrhosis (that is cause unknown) are actually due to steatohepatitis.

Table 1. Causes of fatty liver

Most common
Non-alcoholic fatty liver disease
Common
Part of the spectrum of alcoholic liver disease
(Note: ultrasound may show only fatty liver but diagnosis could be 'alcoholic hepatitis' or cirrhosis)
Uncommon
Rapid weight loss
Jejuno-ileal bypass surgery (also to lesser extent gastric bypass)
TPN
Drugs (tamoxifen, amiodarone, perhexilene).

Diagnosis

The diagnosis is usually made as a result of investigation of abnormal liver tests or may come from an incidental finding at ultrasound performed for other reasons (e.g. investigation of RUQ discomfort). Fatty liver is thought to cause no symptoms but fatigue and ill-defined RUQ discomfort may be present (probably not a direct effect of the condition). The liver is usually of normal size but mild hepatomegaly may be present.

The definition of NAFLD requires minimal alcohol consumption. This 'minimal' level is not well defined. Alcoholic liver disease may occur with only 15 units of alcohol per week. Many cases may be a combination of effects (alcohol plus insulin resistance). It is likely that the liver is more susceptible to the toxic effects of alcohol with increasing levels of obesity. Therefore 5–10U of alcohol per week could be significant if other risk factors for fatty liver are present. The diagnosis of fatty liver also requires the exclusion of other causes of chronic hepatitis (minimum tests are HepBsAg, Hep C Ab, Fe, TIBC and serum ferritin and auto-antibodies – ANA, smooth muscle Ab).

NAFLD should be suspected in patients with risk factors of obesity, hyperlipidaemia and diabetes mellitus. Other features of the metabolic syndrome such as hypertension and increased waist circumference are also useful predictors for NAFLD. Waist circumference may be a better

predictor for fatty liver than BMI. However NAFLD can occur in patients with a normal BMI and in the absence of any known risk factors. Serum ferritin is elevated in half the patients with fatty liver (this is a more common explanation for an elevated ferritin than haemochromatosis – the effect is due to hepatic inflammation and not due to iron accumulation).

Ultrasound is reasonably sensitive for detecting fatty liver (sensitivity 70–85% and specificity of 80–90%) and is a useful screening test. Typically this shows increased echogenicity as the only abnormal feature. In the presence of risk factors for fatty liver, the diagnosis is still possible, indeed likely, even if the ultrasound is normal. Abdominal CT scan is a potentially useful test although accurate diagnosis depends on sensitive calibration of density scores. Fat distribution in the liver is often 'uneven' and can give the appearance of a focal lesion (focal fatty sparing). Often the site of the lesion is helpful (i.e. focal fatty sparing more common in certain areas of the liver) but sometimes imaging with both ultrasound and CT scan is required to make the diagnosis.

The cause of abnormal liver enzyme tests can usually be determined after a careful history and physical examination, a review of medication and alcohol history, appropriate blood tests (as above) and an abdominal ultrasound. The majority of undiagnosed cases after this approach will have non-alcoholic fatty liver disease.

Is a liver biopsy required?

The role of liver biopsy is controversial. The major disadvantage to omitting a liver biopsy in a patient with suspected NAFLD is the loss of information about disease severity and prognosis. No imaging modality can distinguish simple steatosis from steatohepatitis or fibrosis. Cirrhosis may be present with an ultrasound that simply shows fatty liver.

Histology can identify patients at risk for progression to cirrhosis. About 20% of patients with significant steatohepatitis (particularly if there is hepatocyte ballooning, Mallory hyaline or fibrosis) will progress to cirrhosis. Patients with steatosis alone or mild steatohepatitis rarely progress to cirrhosis (probably less than 2%). Accurate figures on prognosis are difficult to find because of the limited studies and the significant bias from tertiary centres with more severe patients. Patients likely to have less severe disease are often not biopsied – this makes studies of long-term outcome difficult to interpret.

The predictors of significant steatohepatitis are age over 45 years, obesity (BMI>28kg/m^2), diabetes mellitus, hypertriglyceridaemia (>1.7mmol/L), and ALT two times over the upper limit of normal.

Predictive models and scoring systems may be useful but none have yet been validated. The risk increases with increasing BMI – over 1/4 of morbidly obese patients will have steatohepatitis and 40% of these patients will progress to cirrhosis.

The potential role of alcohol should not be forgotten and care taken to ensure that the diagnosis is actually non-alcoholic liver disease. Non-alcoholic fatty liver disease (NAFLD) is often histologically and clinically indistinguishable from the liver damage resulting from alcohol excess – the critical information is an accurate alcohol history.

The distinction is very important for treatment and prognosis. The rate of progression to cirrhosis is higher for alcohol-related fatty liver particularly with continued alcohol intake. Patients with type 2 diabetes are more likely to have cirrhosis and have a higher liver-related mortality.

The decision to proceed to liver biopsy needs to be individualised. There is always some value in waiting for six months to see if a more conservative approach to management will lead to a reduction in the elevated liver enzyme tests.

An important part of the diagnostic process is the assessment for other features of the metabolic syndrome. Fasting lipids and glucose (plus perhaps an HbA1c) are essential. A glucose tolerance test may be useful in some patients. Formal testing for insulin resistance – present in most patients with fatty liver regardless of other risk factors – is not currently part of the routine assessment. The detection of fatty liver identifies an individual likely to have insulin resistance. Few would

Key Points

- The cause of abnormal liver enzyme tests can usually be determined after a careful history and physical examination, a review of medication and alcohol history, appropriate blood tests and an abdominal ultrasound. The majority of undiagnosed cases after this approach will have non-alcoholic fatty liver disease.
- No imaging modality can distinguish simple steatosis from steatohepatitis or fibrosis. Cirrhosis may be present with an ultrasound that simply shows fatty liver.
- The predictors of significant steatohepatitis are age over 45 years, obesity (BMI>28 kg/m^2), diabetes mellitus, hypertriglyceridaemia (> 1.7 mmol/L), and ALT two times over the upper limit of normal.
- Non-alcoholic fatty liver disease (NAFLD) is often histologically and clinically indistinguishable from the liver damage resulting from alcohol excess – the critical information is an accurate alcohol history
- An ideal treatment would treat the underlying insulin resistance, prevent the lipid peroxidation (and subsequent inflammatory process) and prevent hepatic fibrosis.

argue against more intensive screening for diabetes, hypertension, and hyperlipidaemia because effective treatment for these disorders is known to reduce cardiovascular mortality. Screening for 'fatty liver' is controversial but may become sensible if treatments can be proven to reduce liver-related deaths. Fatty liver may be a convenient marker for significant insulin resistance but further research is required.

Treatment

Although there is no proven therapy for NAFLD, weight loss and careful management of associated conditions such as diabetes mellitus and hyperlipidaemia is recommended. On a practical level, biopsy results are not generally needed to make these conservative recommendations. On the other hand, demonstration of advanced histologic changes may provide an impetus for some patients to lose weight, gain better control their diabetes mellitus, and cease all alcohol consumption.

In a meta-analysis of the effect of weight loss on fatty liver, all 15 studies included in the analysis demonstrated an overall improvement in various measures of liver disease but more than half of the studies did not report histologic results. The conclusion was that weight reduction is likely to be an effective therapy for non-alcoholic fatty liver but that evidence from good controlled trials is still lacking. One of the most important factors associated with successful weight maintenance is the continuation of appropriate levels of physical activity in the long term. Exercise has an important role in the treatment of visceral adiposity and insulin resistance, i.e. the effect is not just mediated through weight loss. It is important to encourage daily activity with a plan for gradual increase in activity levels. Weight loss should be gradual – not more than 1/2 kg per week. Surprisingly, only modest weight loss (less than 5%) can have a significant effect if combined with regular exercise. Realistic goal setting and regular follow-up is important. Weight-reduction surgery could be considered in severe cases but not using an operation that involves creating a degree of malabsorption (e.g. gastric bypass). Gastric banding has some proven efficacy for severe cases.

An ideal treatment would treat the underlying insulin resistance, prevent the lipid peroxidation (and subsequent inflammatory process) and prevent hepatic fibrosis.

Treatments that improve insulin resistance (lifestyle modifications, some weight-reducing operations and metformin) generally also improve hepatic steatosis. Antioxidants such as vitamin E may have a role but should still be considered investigational. Treatment with a statin is often helpful. If the serum triglycerides are elevated (with a normal serum cholesterol) then bezafibrate may be more effective. Early reports of improved liver function with the use of thiazolidinediones (e.g. Rosiglitazone/Pioglitazone) are encouraging but await definitive trial evidence before these agents can be generally recommended.

Fatty liver, obesity and other causes of liver disease

There is an interaction between hepatic steatosis and other types of chronic hepatitis. A number of studies have now demonstrated an association between increased BMI or visceral adiposity and hepatic steatosis and fibrosis in patients infected with hepatitis C virus (HCV). In overweight patients with chronic HCV, there is an association between increasing insulin levels and increasing hepatic fibrosis, suggesting that host metabolic factors also contribute to disease progression. Similarly, in patients with alcoholic liver disease, elevated BMI and fasting blood glucose are independent risk factors for hepatic fibrosis. A decrease in ALT and insulin levels has been associated with weight loss. A sustained improvement in ALT and insulin levels may be seen with a weight loss of as little as 4–5% body weight. Drug-induced liver disease may also be exacerbated by obesity (e.g. methotrexate).

Summary

Fatty liver has emerged from a neglected condition thought to be innocuous and of no importance into a rapidly evolving field of study. Significant liver disease may occur as a consequence of non-alcoholic fatty liver. The future task is to identify patients at risk of progression (preferably in a non-invasive way) and to provide effective treatments to these at-risk patients. Fatty liver is an important part of the metabolic syndrome and appropriate screening for other components of the syndrome must be made in all patients.

References

1. Harrison SA, Torgerson S, Hayashi PH. The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. Am J Gastroenterol 2003; 98:2042–7.
2. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. Gastroenterology 2002; 122:1649–57.
3. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003; 37:917–23.
4. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346:1221–31.
5. Day CP. Non-alcoholic steatohepatitis (NASH): where are we now and where are we going? Gut 2002; 50:585–8.
6. Chitturi S, Abeygunasekera S, Farrell G, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002; 35:373–9.
7. Weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. American Journal of Medicine 2003; 115(7):554–9.
8. Clouston AD, Powell EE. Non-alcoholic fatty liver disease: is all that fat bad? It Med J 2004; 34:187–191.