Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations

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ABSTRACT

The global increase in the prevalence of obesity has heralded a rise in associated liver injury namely NAFLD (non-alcoholic fatty liver disease). It is estimated that 20–30% of adult populations in developed countries have NAFLD and, although high quality data is currently lacking, the condition is clearly increasing in children also. NAFLD should be suspected in those with commonly available simple clinical signs and biochemistry consistent with insulin resistance. A small number of individuals with NAFLD, often considered a relatively benign condition, will progress to more severe stages of liver disease including NASH (non-alcoholic steatohepatitis) with or without fibrosis, cirrhosis and occasionally hepatocellular carcinoma. NAFLD is also commonly associated with an increased risk of developing Type 2 diabetes and treatable features of insulin resistance such as dyslipidaemia and dysglycaemia. Histological examination of liver tissue remains the only proven method to distinguish between simple steatosis and NASH, a condition far more likely to progress to cirrhosis. Identification of an imaging technique or non-invasive marker to achieve this distinction is therefore much sought after and would allow larger clinical trials and better clinical assessment. Case series and pilot studies of lifestyle advice, insulin sensitizers and other medications have shown improvements in liver histology and serum liver enzymes but robust randomized controlled studies are needed. Furthermore, the cost/benefit ratio of any new therapies, and any potential harms, must be evaluated carefully before being clinically advocated.

INTRODUCTION

Case reports describing the development of liver disease progressing to cirrhosis in obese, low-alcohol-consuming individuals were first published about 40 years ago. However, only in the last 10 years has the importance and scale of the problem been realized. NAFLD (non-alcoholic fatty liver disease), the preferred term linking hepatic involvement to insulin resistance in this scenario, represents a spectrum of disease. Steatosis represents fat accumulation in liver tissue without inflammation and is the earliest recognizable stage. Up to now steatosis has been considered relatively benign. NASH (non-alcoholic steatohepatitis), the next stage, is characterized by steatosis plus hepatocellular injury and inflammation either with or without fibrosis; this group is at far higher risk of...
progression to cirrhosis, the most malign stage. Differentiation between these stages is currently only possible by histological examination in the absence of overt cirrhosis.

The two major risk factors for the accumulation of excess liver fat are obesity/insulin resistance and excess alcohol intake although other causes are well recognized (disorders of lipid metabolism; medications such as amiodarone, diltiazem, steroids, synthetic oestrogens, tamoxifen and highly active antiretroviral therapy; refeeding syndrome; severe weight loss following jejunooileal or gastric bypass; lipodystrophy; total parenteral nutrition; and toxic exposure to organic solvents) [1]. Clinicians will be able to exclude most of these potential causes during history taking although a degree of overlap between NAFLD and fatty liver secondary to alcohol excess probably occurs in some individuals. Previous studies have shown that drinking less than 30 g (3.75 units) of alcohol daily avoids ALD (alcoholic liver disease) [2] and this is sometimes quoted as the somewhat artificial threshold dividing NAFLD from ALD. Others have suggested lower threshold values however [1].

EPIDEMIOLOGY

The prevalence of NAFLD in unselected populations from developed countries is high. Estimates vary between 20 and 30% [3–6] (see Figure 1). Current data suggest that approx. 2–3% of the same population will have NASH [1]. The prevalence of NAFLD increases in parallel with the weight or BMI (body mass index) of the subgroup studied. Prevalence of steatosis in obese individuals (BMI > 30 kg/m²) and morbidly obese individuals (BMI > 35 kg/m²) is estimated at 65–75% [9,10] and 85–90% [9,11] respectively. Furthermore, in obese individuals, the prevalence of NASH increases disproportionately; studies suggest that as many as 15–20% of obese individuals have NASH. Similarly, the vast majority of individuals with NAFLD are either overweight or obese [12]. Studies of NASH patients suggest that between 40 and 95% will be obese, more than half may have Type 2 diabetes mellitus and up to 80% may have dyslipidaemia [13].

DIAGNOSIS OF NAFLD

Clinical findings

Most individuals with NAFLD are asymptomatic and the diagnosis often follows abnormal findings on routine biochemistry prior to commencing medication, abdominal ultrasound performed for another reason or investigation of other features of metabolic syndrome or assessment of cardiovascular risk. Symptoms, when present, may include fatigue and right upper quadrant pain and the most commonly reported clinical finding is hepatomegaly [14]. If advanced cirrhosis eventually develops prior to diagnosis, presentation is similar to other causes, with clinical signs including ascites, splenomegaly, bruising and eventual jaundice. Indeed NAFLD is now recognized as the most common cause of cryptogenic cirrhosis [15] and has been estimated to be the underlying diagnosis in 10% of liver transplant cases.

Routine biochemistry

The overweight or obese patient with abnormal LFTs (liver function tests; see below), with raised or high-normal fasting blood glucose, low HDL (high-density lipoprotein)-cholesterol and elevated fasting triacylglycerols is likely to have NAFLD (see Figure 2 and Table 1). Clinicians are often alerted to the likely presence of NAFLD on the basis of this commonly available clinical information and biochemistry. The co- incidental discovery of fatty liver on abdominal ultrasound will often require the clinician to distinguish between NAFLD and alcohol excess. Although no single parameter can definitively distinguish between the two, the pattern of clinical and biochemical findings will often be informative (see Table 1). Fatty liver due predominantly to alcohol excess is often associated with an AST (aspartate aminotransferase)/ALT (alanine aminotransferase) concentration ratio > 1, unlike NAFLD. Furthermore alcohol excess often results in high HDL-cholesterol together with hypertriglyceridaemia, a pattern not consistent with insulin resistance and NAFLD. Clearly some, perhaps many, individuals may have mixed patterns, owing to both obesity-related and alcohol-related contributions.
The presence of ectopic fat in the liver cell leads to hepatic insulin resistance following the accumulation of intracellular lipid by-products which lead to disturbed glucose metabolism. Clinicians should be alerted to the presence of accumulating liver fat when patients present with a characteristic pattern of biochemical changes (see Table 1 for more details) in conjunction with obesity. FPG, fasting plasma glucose.

Table 1  Common features recognized in ALD and NAFLD

<table>
<thead>
<tr>
<th>Feature</th>
<th>ALD</th>
<th>NAFLD</th>
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<tbody>
<tr>
<td>ALT</td>
<td>→↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>AST</td>
<td>↑↑</td>
<td>→↑</td>
</tr>
<tr>
<td>ALT/AST ratio</td>
<td>ALT/AST &lt; 1.0</td>
<td>ALT/AST &gt; 1.0 (may be reversed in hepatocellular necrosis)</td>
</tr>
<tr>
<td>GGT</td>
<td>↑↑</td>
<td>→↑</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>↑↑</td>
<td>→↑</td>
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<tr>
<td>Weight</td>
<td>↓→↑</td>
<td>↑↑</td>
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<tr>
<td>Fasting plasma glucose</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>↑↑</td>
<td>↓↑</td>
</tr>
<tr>
<td>History of alcohol intake</td>
<td>↑↑ (reliant on patient)</td>
<td>↓↑</td>
</tr>
<tr>
<td>Triglycerols</td>
<td>↑ or ↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
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LFTs and other serum markers

Fatty liver is associated with elevated serum ALT and GGT (γ-glutamyltransferase) concentrations and these commonly measured analytes are now considered surrogate markers of liver fat accumulation. However, neither is sufficiently sensitive nor specific for the diagnosis of NAFLD. ALT and GGT are of most clinical use when combined with clinical findings. It should be noted that the AST concentration can be higher than ALT in cirrhosis, and thus, in individuals with known NAFLD, a rising AST concentration (and reversal of the ALT/AST ratio) is potentially a bad prognostic sign. ALT is clearly associated with being overweight and the strongest determinants of this relationship are increased waist circumference and hyperinsulinaemia, markers of insulin resistance [16]. Increasing ALT comfortably within the usually quoted ‘normal’ range (<30 units/l) has also been shown to correlate with the number of features of metabolic syndrome present [17]. GGT is a relatively non-specific marker of liver disease commonly elevated in NAFLD and it also correlates with features of the metabolic syndrome [18]. Both ALT and GGT appear to correlate with the amount of liver fat present as measured by MRI (magnetic resonance imaging) or ultrasound in children [19,20] and adults [21].

Other markers of interest produced by the liver include SHBG (sex hormone binding globulin), ferritin and plasminogen activator inhibitor-I [22]. However, such markers are not traditionally used to detect NAFLD. Given that these and other hepatic-derived markers, some in common clinical use for other purposes, may be significantly altered with excess hepatic fat content, they may therefore warrant further investigation in assessing hepatic fat content and risk for progression of NAFLD. A number of biochemistry test combinations have been proposed to address the key issue of discriminating NASH from steatosis and results have been variable. A combination of serum adiponectin,
enzymes, those with persistent liver enzyme elevations with moderate or marked elevations in serum liver to have NASH and require biopsy (see below), those Ultrasound should be performed in those more likely to have NAFLD in an individual with clinical features of insulin resistance and mildly elevated serum pressure) and assisted in achieving sustained weight loss and, as pointed out in the British Society for Gastroenterology Guideline for Liver Biopsy [30], the cost of biopsy in all NAFLD cases would be prohibitive. With regard to histological criteria for classification of NAFLD, it is important to note that there is still lack of consensus [1]. There are divergent opinions about which histological features are necessary and their definitions. Features under consideration are the amounts and patterns of fat accumulation, lobular inflammation, fibrosis and the variations found at different ages. Moreover, it must be remembered that there is as yet no licensed treatment for NASH if diagnosed. Evidence of improved outcomes for NASH in prospective clinical trials and imaging modalities with the capability to reliably identify NASH will determine the need for liver biopsy in NAFLD in the future.

**Algorithms to detect individuals with a higher likelihood of NASH**

Published algorithms have attempted to address the issue of detecting individuals with a higher likelihood of NASH. In a study population of 144 patients with NASH, 39 of whom had severe fibrosis, Angulo et al. [31] found that age > 45 years, particularly in the presence of diabetes and/or obesity, was strongly predictive of severe fibrosis. Ratziu et al. [32] investigated 93 overweight patients with abnormal liver function tests and no clear explanation and concluded that age > 50 years, BMI > 28 kg/m², hypertriglyceridaemia and elevated ALT were risk factors independently associated with septal fibrosis. A suggested scoring system combining these
factors was shown to reduce the number of patients requiring liver biopsy [32].

**Novel methods to detect NASH/fibrosis**

Transient elastography (Fibroscan®) is a non-invasive technique used to measure liver tissue stiffness and thereby provide information on the severity of fibrosis. Vibrations are transmitted through the liver by a probe and the speed of the propagating wave, as measured by ultrasound, gives an estimate of liver fibrosis. Some studies have shown a good correlation between the histological grading of fibrosis and Fibroscan® results [33,34] leading proponents to suggest that a number of liver biopsies may be avoided. However significant intra-observer variability has been reported for this device and therefore, at present, Fibroscan® does not appear to be reliable for the diagnosis of advanced fibrosis in patients with fatty liver or visceral obesity [35].

**Who then to biopsy?**

At present it seems most logical to limit patients considered for biopsy to those more likely to have advanced hepatic disease (predictors thereof include age > 45 years, AST/ALT ratio > 1, Type 2 diabetes and BMI > 30 kg/m²) and those with persistent elevations of serum liver enzymes despite adequate therapy for individual features of insulin resistance.

**PATHOGENESIS**

**The source of hepatic fat**

Although increased body fat, as found in obesity, is an important factor predicting insulin resistance, the presence of ectopic fat (in the liver and skeletal muscle), especially within the cells of these organs, is of far greater importance. Fat in the liver can be traced to three sources namely dietary content, de novo synthesis and circulating NEFAs (non-esterified fatty acids) from body fat deposits. Certainly we know that high-fat diets can lead to the development of hepatic steatosis. However, approx. 60% of hepatic fat has been estimated to derive from circulating NEFAs in individuals with NAFLD on a normal fat-containing diet [36]. Peripheral insulin resistance is thought by many to provide increased NEFAs by reduced suppression of adipocyte lipolysis. However, other recent research suggests that this may be too simplistic and other mechanisms may operate [37]. Indeed it has been argued that although circulating NEFAs released from adipose tissue are higher in obese individuals compared with non-obese individuals, systemic values are actually lower when these parameters are expressed in terms of total body fat content; this may therefore represent some form of metabolic compensation by adipose tissue. Either way, increased NEFA flux is associated with hepatic steatosis.

**Hepatic fat as a cause of insulin resistance**

The presence of increased intracellular lipid and lipid by-products leads to important knock-on effects. In skeletal muscle, studies have shown that NEFAs lead to insulin resistance by the following mechanism: in the healthy state, insulin stimulation of IRS (insulin receptor substrate)-1 in muscle cells leads to activation of intracellular PI3K (phosphoinositide 3-kinase) which in turn activates GLUT (glucose transporter)-4 allowing glucose entry. An increase in NEFAs with concomitant increase in intracellular metabolites (diacylglycerol), however, decreases the PI3K activity and decreases glucose cellular entry [38]. The liver is exposed to an excess amount of circulating NEFAs derived from adipose tissue, both peripheral and visceral, and potentially other sources. It has been proposed that a process analogous to that in muscle cells occurs in hepatic cells: in the insulin resistant state, increased circulating NEFAs lead to intracellular accumulation of diacylglycerol which in turn leads to decreased phosphorylation of IRS-2 via activation of a serine kinase cascade (see Figure 2). The decreased activity of PI3K leads to increased, dysfunctional cellular glucose production. Inflammatory pathways may also contribute to insulin resistance as discussed below.

**Hepatic fat as a cause of inflammation?**

There is good evidence of an association between hepatic steatosis and chronic inflammation, and a key player appears to be NF-κB (nuclear factor κB). NF-κB is a transcription factor activated upstream by IKKβ [IκB (inhibitory κB) β]. In animal models it has been shown that high-fat diet with resultant hepatic steatosis leads to increased NF-κB signalling in the liver [39]. NF-κB activation then induces the production of local and systemic inflammatory mediators, such as TNF (tumour necrosis factor)-α, IL (interleukin)-6, IL-1β which may play a role in the progression of NAFLD and also leads to activation of Kupffer cells, and macrophages within liver tissue. In the same study [39] there is evidence that inflammation, in the form of isolated increased NF-κB expression in rat liver (achieved in normal weight IKK-β transgenic mice with resultant doubling in IKK-β and NF-κB expression), can lead directly to insulin resistance [39]. This evidence is supportive of a single process leading to NAFLD progression unlike the two-hit theory which has also been proposed. In the two-hit model a primary insult leads to fat accumulation and a separate insult is required for progression to inflammation and fibrosis.

**FACTORS THAT PREDICT PROGRESSION OF NAFLD AND DISTINGUISH BETWEEN STEATOSIS AND NASH**

At present there are no studies of adequate power using sequential liver biopsies in those with simple steatosis to
identify features that might predict progression to NASH and cirrhosis. Published cohort studies with physical and biochemical features in groups with varying stages of liver disease have at least allowed comparisons to be made and algorithms have been suggested as discussed above. However, conclusions from such studies are not consistent. For example, in a recent Korean study comparing groups with steatosis and NASH \((n = 39)\), only differences in mass reached significance whereas routine biochemistry did not \[40\]. The ability of HOMA-IR, a measure of insulin resistance, to identify NASH has also been investigated; in one study HOMA-IR > 5.8 gave an odds ratio of 4.18 in obese patients prior to gastric bypass surgery \[41\] and in another NAFLD cohort the AUC (area under the curve) of the ROC (receiver operator characteristic) was 0.757 \[23\]. Clearly more data is required to help distinguish between different NAFLD stages and to predict disease progression. Although excess calorie intake is itself inevitably a risk factor for NAFLD, dietary composition may also be relevant. In a small study comparing dietary intake of 25 non-diabetic and non-obese individuals with NASH and 25 age-, gender- and BMI-matched controls, the intake of those with NASH contained significantly lower levels of vitamin E, vitamin C and polyunsaturated fats plus significantly more saturated fat \[42\]. Other possible risk factors for NAFLD progression include family and race. There is evidence of family clustering of NASH \[43\]. This is not unexpected given the known strong family histories of Type 2 diabetes and obesity. Furthermore, studies of young, healthy offspring of parents with Type 2 diabetes (and therefore at increased risk of developing diabetes themselves) have shown that they already have increased plasma NEFAs compared with controls. An observational study has also reported a relatively higher incidence of cryptogenic cirrhosis and cirrhosis attributed to NASH in Hispanics but a lower incidence in African-Americans despite similar levels of Type 2 diabetes in both groups \[44\]. The latter observation is in keeping with better-than-expected lipids (low triacylglycerols and high HDL-cholesterol) in African-Americans despite a greater incidence of diabetes.

**Genetics and NAFLD?**

The genetic contribution to NAFLD remains to be fully elucidated but wide-ranging research is ongoing. Indeed the broad range of NAFLD phenotype found in individuals with similar metabolic characteristics points to a complex genetic contribution. Examples include microsomal triacylglycerol transfer protein gene \[45\] and TNF\(\alpha\) polymorphisms \[46\]. However, such genetic studies are small and require much larger studies for confirmation.

**NAFLD IN CHILDREN**

Obesity in children is recognized as a major current and future health problem. As in adults, NAFLD is emerging as a significant complication. High-quality studies of NAFLD prevalence in unselected groups of children are lacking. Existing studies have used different techniques (ultrasound, elevated serum ALT concentration, liver histology) making comparisons difficult. Nonetheless, studies from the U.S.A. and Asia suggest a prevalence of between 2.5 and 9.5% \[47–49\]. Similar limitations affect studies of the overweight/obese subgroup, not to mention variations in definitions of childhood obesity. Studies suggest a prevalence of anything up to 80% in the obese. NAFLD is more common in boys compared with girls, and white and Hispanic children compared with black children \[50\]. The natural history of NAFLD is poorly understood in children. As in adults, cirrhosis may develop, although rarely. Cases of HCC have also been reported in adults who had NAFLD as children \[51\]. The histological pattern of NASH in children often differs from that in adults as inflammation and fibrotic changes are frequently found in portal or peri-portal regions \[52\]. The differential diagnosis of NAFLD in children also differs from adults, lying primarily between metabolic and inflammatory conditions. The use and timing of liver biopsy in children is contentious with a recent guideline stating that biopsy should be considered early especially in those with markedly abnormal LFTs \[53\]. There is also little evidence demonstrating a benefit of therapy for NAFLD in children.

**TREATMENT**

At present no medication or surgical procedure has been approved for treating NAFLD and there is no evidence yet showing the impact of any treatment modality from prospective double-blind randomized trials on important long-term outcome measures, such as cirrhosis and HCC. Until such data is forthcoming, the current focus of therapy must therefore remain in encouraging reduction in future diabetes risk (via increased activity and better diet, potentially facilitating weight or waist circumference reduction) and cardiovascular risk (appropriate treatment of dyslipidaemia and hypertension in those at significantly elevated risk). Nevertheless, numerous intervention studies have shown improvements in liver enzymes and histology suggesting that it is likely that beneficial therapy for NAFLD will be confirmed before long. Given the findings of small studies described below, the listed therapies should certainly not be withheld in the presence of NAFLD.

**Lifestyle-mediated weight loss**

Lifestyle-mediated weight loss, through reduced caloric intake and increased activity, is generally recommended as the logical method to reduce liver fat content. There is no data from randomized controlled studies to support this position at present, however. A number of published
case series have shown improvements in LFTs, hepatic ultrasound or histological staging but without comparison with a control group. Examples include two studies examining the effect of weight loss on LFTs, in which it was found that in those who lost a significant amount of weight (± 10 %), LFTs improved significantly compared with those who did not lose significant weight, suggesting that a reduction in hepatic fat content is associated with weight loss [54,55]. In a study comparing intensive lifestyle modification with no lifestyle changes over a period of 3 months (n = 25) in overweight patients with NAFLD, the treated group showed improvements in all histologically measured parameters, although these did not reach significance [histological activity index of steatosis in the treatment group fell from 2.3 to 1.3 (P = 0.05); histological activity index did not change in the control group: 2.5 and 2.6 respectively] [56]. Readers are directed to a recent review which examines the impact of diet, exercise and combined diet and exercise on NAFLD [57].

**Medication**

The impact of various medications on NAFLD including weight-loss drugs and oral hypoglycaemic agents has been studied. These studies have usually been small and often compromised by the lack of a control group.

**Weight-loss drugs**

In published pilot studies, treatment with orlistat, a lipase inhibitor which reduces fat absorption, has lead to improvements in LFTs, ultrasound findings and hepatic histology [58,59]. In another study comparing orlistat (n = 12) and sibutramine (n = 13), an enhancer of satiety mediated by central inhibition of serotonin and noradrenaline reuptake, treatment with both drugs lead to improvements in LFTs and reduced liver fat on ultrasound [60].

**Oral hypoglycaemic agents**

Insulin-sensitizing agents, namely the thiazolidinediones (glitazones) and metformin, have been investigated. Glitazones are generally considered to redistribute fat away from ectopic sources (in particular the liver) to subcutaneous areas but overall weight is often increased (markedly in some patients) and glitazones can also lead to peripheral oedema and heart failure [61,61a]. Furthermore, although pioglitazone appears to confer cardiovascular benefit, recent studies have suggested that rosiglitazone may slightly increase cardiovascular risk [61,62]. In an uncontrolled study of treatment with rosiglitazone (8 mg daily for 48 weeks; n = 30) [63], ALT concentrations fell significantly from 104 units/l to 42 units/l and histological grading improved despite weight gain in most patients. Indeed, in the 22 individuals with NASH prior to therapy, ten no longer had NASH post-treatment. However, 6 months after the trial was completed and therapy stopped, ALT concentrations had returned to pre-treatment levels. In another uncontrolled study, treatment with pioglitazone (30 mg daily for 48 weeks; n = 18) resulted in significant reductions in serum ALT and liver fat content [64]. In a 6 month randomized controlled study comparing hypocaloric diet plus placebo with hypocaloric diet plus pioglitazone (45 mg daily) in 55 patients with biopsy-confirmed NASH and either Type 2 diabetes or impaired glucose tolerance [65], the pioglitazone group had a significant reduction in serum ALT and significant reductions in hepatic steatosis and necroinflammation (though not fibrosis) compared with the diet-only treated group. Treatment with metformin has resulted in smaller reductions in ALT and histological improvements have been less consistent [66,67]. Further large studies are required in this area.

**Implications of NAFLD for other commonly used medications**

Numerous patients with NAFLD are likely to be considered for statin therapy due to concomitant dyslipidaemia and increased cardiovascular risk. Statin therapy in NAFLD certainly appears safe in the presence of NAFLD and should not be avoided due to mildly abnormal transaminase levels [68]. There is also some evidence of improvement in liver histology on statin therapy from a small placebo-controlled study recently published [69]. Vitamin E therapy has produced variable results [67,70] and fibrate therapy has not shown benefit thus far [71]. In one of the only placebo-controlled studies so far, combination therapy with UDCA (ursodeoxycholic acid) with vitamin E for 2 years resulted in a significant reduction in hepatic steatosis [72]. UDCA therapy alone did not improve histology, although serum ALT was reduced. In two small studies, treatment with the angiotension II blocker, losartan, also led to improvements in liver histology [73,74].

**Surgery**

Recently published studies with follow-up over 18–24 months have shown that obesity surgery can lead to improvement in NAFLD staging or resolution thereof. Following laparoscopic Roux-en-Y bypass surgery and concomitant weight loss (mean 50 kg) and evaluated by liver biopsy, Liu et al. [75] found considerable improvements in the prevalence of steatosis (90% pre-operatively to 2.9% post-operatively), hepatocellular ballooning (58.9% pre-operatively to 0% post-operatively) and centrilobular fibrosis (50% down to 25%) [75]. In a similar study, Furuya et al. [76] found similarly impressive reductions in steatosis, fibrosis and hepatocellular ballooning. In this latter study on a group of 18 patients, NASH resolved in 84% of patients and steatosis in 75%. Laparoscopic-adjustable gastric banding with resultant weight loss has also led to promising improvements in liver histology [77,78].
NAFLD AND THE PREDICTION OF INCIDENT TYPE 2 DIABETES

The importance of NAFLD recognition should be considered in terms of treatment options and also possibilities of disease prediction. As discussed above, it is possible that therapies which improve NAFLD staging or resolve steatosis may lead to improved patient outcome. Secondly, the presence of NAFLD is associated with an increased risk of future-onset Type 2 diabetes and potentially cardiovascular disease. If not already diagnosed with diabetes, individuals with NAFLD are revealing themselves to be at elevated risk for diabetes and therefore warrant lifestyle advice. Furthermore, because of potentially increased cardiovascular risk, they warrant measurement of lipids and blood pressure to ascertain level of cardiovascular risk.

Type 2 diabetes

There is clear evidence that markers associated with fatty liver predict future development of Type 2 diabetes. Indeed ALT, a reasonable marker of fatty liver, remained independently associated with the development of Type 2 diabetes in WOSCOPS (West of Scotland Coronary Prevention Study) over 5 years [17]. Furthermore, sustained moderate elevation in ALT over time was associated with conversion into diabetes over 18 months in men in WOSCOPS [79] more strongly than a change in any other measured biochemical marker. In a study of 3500 non-diabetic men, Wannamethee et al. [80] concluded that increasing levels of not only ALT but also GGT, even within the normal range, are independent predictors of Type 2 diabetes.

CONCLUSION

NAFLD, the accumulation of ectopic fat in the liver with possible progression to NASH and cirrhosis, is increasingly common and clearly linked to obesity and insulin resistance. Individuals with NAFLD are at higher risk of developing Type 2 diabetes since liver fat impedes liver glucose metabolism. Furthermore, individuals with NAFLD may have an increased risk of cardiovascular disease and so all should receive lifestyle advice and conventional cardiovascular risk factor screening. There is presently no clear justification to carry out ultrasound measurements in the majority. The combination of clinical findings and routine blood results will help to distinguish between NAFLD and ALD in many cases. The diagnosis of NASH is important given the risk of progression to cirrhosis and HCC. At present, however, histology is the only method to reliably diagnose NASH. Liver biopsy should be considered in those at higher risk of NASH and liver fibrosis. Novel biochemical markers and imaging techniques able to better identify those with NASH are highly sought after to improve relevant research and patient management. Although a number of therapies have resulted in improved serum ALT concentration and histology, prospective studies, and proper consideration of risks, benefits and costs, are required before these therapies can be recommended to treat NAFLD.

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