Management of non-alcoholic fatty liver disease in the context of diabetes

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It is widely recognised that, based on liver blood tests, people with diabetes commonly have mild abnormalities of the liver. The majority of these individuals will have fatty liver. There have been dramatic advances in the understanding of the inter-relationship of liver fat (steatosis) and insulin resistance over the last few years. It is accepted that non-alcoholic fatty liver disease (NAFLD) goes hand in hand with features of the metabolic syndrome. Further understanding of NAFLD has shown that this liver condition can be progressive: in some people leading to cirrhosis, liver failure and primary liver cancer. This article highlights our current understanding of NAFLD and summarises the management issues in this condition, particularly in the context of diabetes.

There has long been an awareness that a large number of people with diabetes have mildly abnormal liver function, and that, for the majority, there is no evidence of significant liver disease, no risk factors for chronic viral hepatitis and no history of excessive alcohol consumption. Liver biopsies, if undertaken in this cohort of individuals, have demonstrated the presence of fat in the liver (known as fatty liver or steatosis). Initially thought to be an entirely benign process from the liver perspective, from the mid-1990s onwards it has become clear that a sub-group of those with fatty liver also have inflammation and scarring, and that in some individuals with inflammation or scarring followed over a number of years, progression of this scarring can occur, ending up in cirrhosis in a minority (Powell et al, 1990; Teli et al, 1995).

In parallel, as the mechanisms underlying type 2 diabetes have become better understood and the concept of systemic insulin resistance evolved, it rapidly became clear that there was an over-representation of features of the metabolic syndrome (also known as syndrome X or insulin resistance syndrome) in individuals with fatty liver (reviewed in Haque and Sanyal, 2002). The defined link was established with detailed studies of insulin sensitivity in patients with fatty liver, with the finding of an almost ubiquitous reduction in systemic insulin sensitivity in these individuals (Bugianesi et al, 2004).

As the concept of insulin resistance as the underlying process in the progression to frank type 2 diabetes has evolved, it has become accepted that fatty liver is one more component to add to the obesity, hypertension, dyslipidaemia and impaired glucose tolerance associated with type 2 diabetes. There is general agreement of the central importance of fat deposition in the liver in systemic insulin resistance, though how this ties in with other ectopic fat deposition (for example, in skeletal muscle) has not been fully elucidated. The fact that non-alcoholic fatty liver disease (NAFLD) is the commonest cause of abnormal

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liver function test results (LFTs), affecting 20–40% of populations in Western societies (Clark et al, 2002), and the increasing recognition that end-stage liver disease can result from this process, has meant that the interest in fatty liver has grown exponentially in recent years.

NAFLD: A natural history

Fatty liver, when first described, was thought to be an entirely benign process (Powell, 1990). Teli et al (1995) described progression of non-alcoholic steatohepatitis (NASH) in a proportion of an already small study group, whereas those with fat alone (steatosis) did not develop a progressive liver disease as demonstrable by histology. More recent evidence has reinforced this differentiation between steatosis and NASH, with evidence of increased liver-related mortality in those with NASH but not those with steatosis (Dam-Larsen et al, 2004; Ekstedt et al, 2006).

Are all those with fat alone fine and those with NASH going to develop progressive liver disease? This is at present unknown, but long-term (longer than 15 years) follow-up of a large cohort of fatty liver patients with no NASH did not suggest progression to severe liver disease (Dam-Larsen et al, 2004).

Although evidence that NASH is a potentially progressive liver lesion is now robust (Ekstedt et al, 2006), it is also clear that progression of NASH does not occur in all patients. Fassio et al (2004) looked at 22 people with NASH who had undergone serial liver biopsies separated by a median of 4.3 years and found that discernible progression of fibrosis occurs in around one-third within this time frame. Adams et al (2005) studied 103 patients with NASH biopsied twice (median interval 3.2 years) and found a similar proportion had progressed.

The question, then, becomes why do only a minority get progressive liver disease and how can one predict those that will? This is currently not known, but evidence suggests that the presence of frank type 2 diabetes is associated with a greater risk of progression (Adams et al, 2005). This would be consistent with all the evidence linking the degree of insulin resistance or the number of features of the metabolic syndrome with more active NAFLD (*Table 1* lists the features that

make up metabolic syndrome). The presence of diabetes is also known to increase the risk of subsequent development of primary liver cancer (El-Serag et al, 2004).

Clinical assessment

In assessing a person with diabetes and abnormal LFTs, it is important to be clear whether one is dealing with a condition other than NAFLD. The presence of auto-immune liver diseases, hereditary and chronic viral liver diseases are all important to determine and can frequently be uncovered by screening of asymptomatic individuals with abnormal LFTs. It is worth noting at this point that there is good evidence now for a link between diabetes and chronic hepatitis C virus infection, with some of the viral proteins acting directly to induce insulin resistance (Allison, 1994; and reviewed in: Ratziu et al, 2005). In addition, haemochromatosis is well known to cause both liver disease and diabetes, with much rarer hereditary disorders such as maturity onset diabetes of the young-3 (MODY-3) and glycogen storage disease type 1 also needing to be considered, as multiple liver adenomas and diabetes can be seen in both of the latter (Bacq et al, 2003). (*Table 2* lists the most common liver diseases linked to diabetes.)

From the point of view of NAFLD, patients are most frequently asymptomatic and clinical examination will often demonstrate no signs of significant liver disease. Positive findings of palmar erythema, hepatomegaly or splenomegaly are found in a significant proportion of people and merit further evaluation of the liver.

Assessment of liver disease:
The role of liver biopsy

Liver biopsy has for many years been considered the gold standard for assessing the majority of forms of parenchymal liver disease. The important issues in NAFLD are determining whether there is simply steatosis or NASH, and also what degree of fibrosis is present. A liver biopsy is often used to answer these two questions. A further important consideration is whether there is an additional or alternative diagnosis to NAFLD, and here also liver biopsy is a unique tool – particularly in the context of people with asymptomatic

mild abnormalities of liver function; however, the utility of a liver biopsy and its impact on management need to be considered.

Assessment of liver disease: The role of non-invasive markers of liver disease

This is an area of huge interest as a liver biopsy is an unpleasant procedure with associated risks and significant healthcare costs. Work to assess the stage of liver disease non-invasively has focused on two areas: imaging and blood tests combined into algorithms. These approaches are appealing in NAFLD, as this condition is very common, often asymptomatic, with only minor abnormalities of liver function; and the liver disease itself, if progressive, has an indolent course, which needs to be followed over a period of time.

Algorithms based on blood tests and phenotypic parameters, such as the NAFLD score and enhanced liver fibrosis (ELF) panel have shown promising results in terms of sensitivity for determining those with severe fibrosis (Angulo et al, 2007; Guha et al, 2008), but have poorer reliability in determining moderate or milder forms and have not yet been found to be able to predict those with potentially progressive liver disease, which is one of the key issues in this area.

Assessment of liver disease: The role of imaging

Ultrasound has been found to have a sensitivity of around 90% in determining the presence of fat in the liver. There is interest in this as fat in the liver is a marker of insulin resistance and as such may predict a consequent increased risk of developing type 2 diabetes and cardiovascular disease (reviewed in: Targher et al, 2008). Computed tomography imaging can also be set to assess liver fat content, as can magnetic resonance imaging, the latter being able to quantify liver fat (reviewed in: Mehta et al, 2008).

In terms of clinical management, however, the key issue is not the degree of liver fat, but whether there is associated inflammation, scarring or both, and none of these modalities are at present able to determine this (Saadeh et al, 2002). The use of ultrasound elastography is widely reported as being informative for a variety of liver diseases including NAFLD. This modality can be compromised, however, by the presence of steatosis and also by a raised BMI, both common in people with type 2 diabetes.

Magnetic resonance elastography has been found to have high sensitivity and specificity (Huwart et al, 2008), but further work is needed before the use of this modality has wide utility, given cost and availability.

Treatment

As there are currently no specific treatments for NAFLD, the therapies that target the underlying insulin resistance hold the most promise (*Table 3*). Given the indolent nature of the condition, and the fact that it only appears to progress in a minority of cases, large-scale long-term randomised controlled trials of treatment are required to show an important change in disease. The trials published so far, with a few exceptions, have determined response after no more than 12 months' treatment (Bugianesi et al, 2005; Belfort et al, 2006; Ratziu et al, 2008).

In the author's opinion, lifestyle changes, as for all those with the metabolic syndrome, should be the cornerstone of the treatment for those with NAFLD. There is evidence for the benefit of weight loss and physical activity in terms of improving insulin resistance, though there is, as yet, no proven long-term benefit on the NAFLD itself (reviewed in: Rafiq and Younossi, 2008). In those with more severe obesity who undergo bariatric surgery, there is now solid evidence for histological benefit in NAFLD (Shaffer, 2006).

Metformin has been investigated in small studies in NASH and found to decrease liver fat levels (Bugianesi et al, 2005). The more powerful insulin sensitisers, the thiazolidinediones (TZDs), have demonstrated a greater improvement in liver fat profiles, concomitant with a reduction in inflammation and fibrosis, in a randomised controlled trial (Belfort et al, 2006; Ratziu et al, 2008; the latter showed no significant effects on fibrosis).

Safety of medications in the context of NAFLD

As already mentioned, people with type 2 diabetes frequently have a mild abnormality of liver function. These same people require modification of cardiovascular risk factors and adequate control

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Table 3. Treatment options for non-alcoholic fatty liver disease.

Weight reduction
- Diet
- Orlistat
- Sibutramine
- Bariatric surgery

Insulin sensitisers
- Metformin
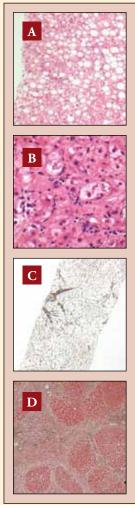- Thiazolidinediones

Lipid-lowering agents
- Statins
- Fibrates

Anti-oxidants
- Vitamin E
- Betaine
- *N*-acetylcysteine

Anti-inflammatory agents
- Anti-tumour necrosis factor-α antibodies
- Pentoxifylline

*Appendix 1. (A)
Steatosis – fat alone
with no inflammation
or fibrosis (low power);
(B) Non-alcoholic
steatohepatitis (NASH)
– fat with inflammation
(high power); (C)
Mild fibrosis in NASH
– reticulin stain showing
fibrosis pattern in mild
disease (low power);
(D) NASH cirrhosis
– islands of hepatocytes
surrounded by fibrosis
(medium power).*

of their diabetes. There may be some concern over statin use in people with abnormal LFTs; however, there is now convincing evidence that statin hepatotoxicity is extremely rare, and possibly not more frequent than that observed with placebo, and also that the presence of pre-existing abnormalities of liver function does not increase the risk of statin hepatotoxicity (Chalasani et al, 2004; de Denus et al, 2004). Such agents should therefore be used where indicated in people with type 2 diabetes. Monitoring of LFTs is prudent.

In terms of insulin sensitisers, metformin has been shown to be beneficial in reducing liver fat and improving liver blood test results, and there is evidence of histological benefit of pioglitazone in NASH patients with impaired glucose tolerance or frank type 2 diabetes (Belfort et al, 2006), with no indication of the rare but occasionally fatal hepatotoxicity of the original TZD, troglitazone.

Discussion

It is clear that the evolving epidemic in Western societies of obesity and consequent type 2 diabetes are resulting in a rapidly increasing prevalence of NAFLD. While end-stage liver disease with or without primary liver cancer is currently being seen most frequently in the seventh and eighth decades of life, this will in the future be seen in larger numbers in younger adults. Overall, the result will be an increasing burden on healthcare resources relating to liver disease (including liver transplantation) as well as to cardiovascular disease and other end-organ damage in this group. As a greater understanding of the processes underpinning the evolution of insulin resistance develops, it is hoped that newer therapies aimed at increasing insulin sensitivity can be introduced to change the natural history of NAFLD and the metabolic syndrome as a whole. In terms of NAFLD itself, it is likely that therapies that improve insulin sensitivity will benefit the liver and these in combination with specific anti-fibrotic treatment may retard or prevent advanced liver disease.

Monitoring of disease severity and response to treatment will be aided by further improvements in the power of non-invasive means of assessing the fibrosis in NAFLD and whether an individual is at risk of progressive liver damage.

Conclusions

An awareness of the potential liver diseases seen in individuals with diabetes is essential for those managing diabetes in primary or secondary care. Liver blood test abnormalities may be seen in a large proportion of people with type 2 diabetes patients in particular; with by far the commonest explanation for these being NAFLD. Fatty liver should be considered as part of the metabolic syndrome. Specific therapies for the liver disease itself are currently lacking and clinical management should be directed at treating the underlying insulin resistance. However, recognition of the fact that diabetes and obesity are independent risk factors for advanced liver disease, including cirrhosis and primary liver cancer, can lead to earlier detection of such conditions with consequent improved treatment options. ■

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