A PRIMARY CARE APPROACH TO NON-ALCOHOLIC FATTY LIVER DISEASE

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been described as the hepatic manifestation of the metabolic syndrome and its prevalence has increased together with obesity and diabetes rates worldwide[1,2]. Population-based studies describe the prevalence of NAFLD to be between 14-31% in Europe and America[3]. In Asian-Pacific countries, it been estimated at 9-30%, with higher rates of 10-80% amongst obese patients, 30-90% in patients with diabetes and 15-69% in patients with dyslipidaemia[4].

NAFLD is a common medical condition, especially among patients who are have the metabolic syndrome, and will frequently present to the family physician. The purpose of this clinical review is to outline an approach to the diagnosis and management of NAFLD in primary care.

METHODOLOGY

PubMed searches were conducted for publications related to NAFLD using the keywords "non-alcoholic fatty liver disease" or "non-alcoholic steatohepatitis" and "epidemiology", "natural history", "pathophysiology", "diagnosis", "treatment", "follow-up" or "surveillance". The search was limited to articles in English that were published between 2004 and 2009. A total of 596 articles were obtained, of which 28 were used in this review. In addition, 16 referenced publications were included from Pubmed obtained articles used in the review.

DEFINITION AND NATURAL HISTORY OF NAFLD

Definition and pathophysiology

The term NAFLD is used to describe a condition of fat accumulation exceeding 5 to 10% in the liver, in the absence of excessive alcohol intake and other specific causes of hepatic steatosis[3]. Normal alcohol intake is defined as less than 20g per day or 14 units per week[5]. Other conditions that may cause hepatic steatosis are included in Table 1[3,6]. NAFLD results from a combination of insulin resistance, abnormal secretion of leptin and adiponectin, which regulate lipid and glucose metabolism, and increased release of inflammatory cytokines such as tumour necrosis factor alpha and interleukins[7].

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Table 1. Causes of Hepatic Steatosis apart from NAFLD [3,6]

Conditions	Examples
• Drug induced	Glucocorticoids, tamoxifen, amiodarone, diltiazem, methotrexate or highly active anti-retroviral therapy
• Nutritional	Malnutrition, rapid weight loss, total parenteral nutrition
• Gastrointestinal disease	Inflammatory bowel disease, jejunal diverticulitis with bacterial overgrowth
• Metabolic causes	Disorders of lipid metabolism, such as abetalipoproteinemia lipodystrophy
• Occupational and environmental exposure to toxic substances	Phosphorus, toxic mushrooms

Natural history and associated complications

NAFLD comprises two entities: hepatic steatosis, with liver histology showing only hepatic steatosis, and non-alcoholic steatohepatitis (NASH), where additional hepatic inflammation or fibrosis is present[5]. Hepatic steatosis runs a benign course while NASH, first described in 1980, has the potential to progress to liver cirrhosis and hepatocellular carcinom[8]. Studies have shown that 1 to 20% of hepatic steatosis progresses to NASH, of which 5-38% develop advanced fibrosis and 2-30%, cirrhosis. Of those with cirrhosis, 11-25% develop hepatocellular carcinoma[1,3,9,10,11]. In addition to hepatic complications, NAFLD is also a risk factor for future cardiovascular death events in individuals with Type 2 diabetes and increased risk of chronic kidney disease and diabetic retinopathy, independent of other known risk factors[12,13].

DIAGNOSING A PATIENT WITH NAFLD

Clinical Presentation

A diagnosis of NAFLD is usually suspected when a patient has raised alanine aminotransferase (ALT) and aspartate transaminase (AST) levels or a diagnosis of "fatty liver" on abdominal ultrasound (US)[14]. Clinically, the patient may complain of fatigue or right upper quadrant discomfort and examination may reveal hepatomegaly. Clinical features of liver cirrhosis and portal hypertension are rare[15].

Pertinent clinical history

When abdominal US shows "fatty liver", excessive alcohol consumption and other causes of hepatic steatosis should be excluded with a detailed history on long-term alcohol intake, medication use, recent weight changes, a past medical and occupational history. When ALT levels are raised, in addition to excessive alcohol consumption, it is important to exclude a history of Hepatitis B or C virus infection and ingestion of drugs

including herbal medications. Less common causes for raised ALT levels include autoimmune hepatitis, celiac disease, Wilson's disease, alpha-1-antitrypsin deficiency, hepatic malignancies, hepatobiliary infections and biliary tract disease[16].

Next, the patient should be screened for metabolic risk factors as most patients with NAFLD have one or more of these factors. They include hyperglycaemia (impaired fasting glucose, Type 2 diabetes), hypertension, increased waist circumference or obesity (body mass index (BMI) greater than 25 kg/m2) and hypertriglyceridaemia or hypercholesterolaemia[12,17,18].

Laboratory and radiological investigations

Currently, the gold standard for diagnosis of NAFLD is liver biopsy because only histology differentiates between benign hepatic steatosis and NASH[17,19]. However, requiring liver biopsy for diagnosis of all cases of NAFLD would be impractical due to potential overwhelming of gastroenterological services, patient acceptability, cost and risks of complications such as pain, intraperitoneal bleeding and death (1 in 10000). Biopsy interpretation of NAFLD also has inadequacies due to sampling variability and inter-observer variations in interpretation. Finally, due to the current lack of evidence for definitive treatment of NASH, the benefit of liver biopsy in the diagnosis of NASH may not outweigh its risks[12,15].

As such, it is acceptable that the diagnosis of NAFLD be made based on the presence of risk factors for metabolic syndrome and the finding of hepatic steatosis on radiological investigation, after excessive alcohol intake and other disorders have been excluded[15]. Abdominal US is recommended for evaluation of hepatic steatosis and detection of biliary tract disorders or focal hepatic disease. Hepatic steatosis is diagnosed if two out of three findings are present: Diffused increase of echogenicity in the liver that is greater than that in the kidney or spleen, vascular blurring and deep attenuation of ultrasound signal[16]. Abdominal US has a sensitivity and specificity of 89% and 93% and is affordable. However, US and other radiological modalities only detect hepatic steatosis when more than 33% of fat is present in the liver and are unable to differentiate between simple steatosis and NASH. Computed tomography (CT) or magnetic resonance (MRI) may be considered if US is not diagnostic, especially in obese individuals and cases of focal fatty changes[14,20].

Liver biopsy is recommended for individuals with uncertain diagnosis, persistent elevations of ALT (more than 3 times upper limits of normal: normal < 30 unit/L) despite adequate therapy for features of metabolic syndrome and those who are at higher risk of hepatic fibrosis[14,15]. The predictors for hepatic fibrosis include age more than 45 years, Type 2 diabetes, BMI more than 30 kg/m2, AST: ALT ratio of more than 1 and low platelet count[1,15,21]. Biomarkers are being developed for the diagnosis of NASH or NASH-associated hepatic fibrosis, however, the accuracy of these tests are currently limited and are not fully validated for clinical use[10].

Currently, laboratory tests contribute minimally to the diagnosis of NAFLD but they should be done to assess liver function, exclude other causes of liver disease and screen for metabolic risk factors. The recommended laboratory investigations are outlined in Table 2.[1,6,15,16,21,22]

TREATMENT

Patients should be advised to cease ingestion of alcohol and drugs that may worsen liver function[7]. Treatment of NAFLD is currently focused on weight reduction and management of cardiovascular risk factors. The search for effective pharmacological treatment is still preliminary and drugs are currently not recommended for specific treatment of NAFLD[14,16]. Current available evidence on relevant investigational treatments is summarized below.

Weight Management

Weight reduction in obese patients of 10% from the baseline weight has been shown to reduce ALT levels and hepatomegaly[1,4]. Recent studies have shown that even smaller amounts of weight loss are beneficial in reducing insulin resistance and reversing hepatic steatosis on US[21,23,24]. However,

Table 2. Laboratory Investigations for the assessment of NAFLD[1,6,15,16,21,22]

Tests for Liver Function	Notes
• ALT, AST	Absence of raised ALT does not exclude NAFLD
• AST: ALT ratio	AST: ALT ratio > 1 could indicate excessive alcohol intake or advanced liver fibrosis
• GGT	Raised GGT levels are seen in NAFLD and excessive alcohol intake
• ALP[a]	Raised ALP indicates cholestasis or liver injury
• Serum bilirubin, albumin, PT[b]	Low bilirubin, albumin and prolonged PT indicates hepatic decompensation
• Full blood count	Low platelet count is a risk factor for hepatic fibrosis. Raised white cell counts may indicate infection
Tests for other liver diseases	
• HBsAg, Anti-HCV	Screening tests for Hepatitis B and C virus infections
• Antinuclear antibody	Test for autoimmune hepatitis
Consider these tests:	
• Anti-smooth muscle antibody	Test for autoimmune hepatitis
• Anti-mitochondrial antibody	Test for primary biliary cirrhosis
• Serum caeruloplasmin	Test for Wilson's disease
• Alpha-1-antitrypsin levels	Test for alpha-1-antitrypsin deficiency
• Transglutaminase antibodies	Test for celiac disease
Screen for metabolic risk factors	
• Fasting blood glucose or oral glucose tolerance test (OGTT)	Screen for impaired fasting glucose, impaired glucose tolerance or Type 2 diabetes
• Fasting lipids	Screen for hypertriglyceridaemia, high LDL[c] and low HDL[d] levels

[a]ALP: Alkaline phosphatase, [b]PT: Prothrombin time, [c]LDL: Low density lipoprotein, [d]HDL: High density lipoprotein

weight loss should be gradual as losing more than 1.6 kg per week has been shown to potentially worsen steatohepatitis and result in gallstones[25]. Weight loss may be achieved through an exercise and diet program: Aerobic exercise improves insulin resistance independent of weight loss, while calorie-restricted diets reduce weight and diets low in saturated fat and high in fibre reduce insulin resistance[1,4].

The effects of weight loss drugs such as orlistat and reductil on NAFLD have only been examined in pilot studies. Two studies conducted showed that six months of treatment with orlistat or sibutramine, in combination with a low caloric diet, improve insulin resistance, transaminases and US findings. One of the studies also showed improvement in inflammation on histology and reductions in triglycerides and LDL levels[26,27]. Bariatric surgery for the treatment of morbid obesity (BMI greater than 40 or BMI greater than 35 with co-morbid conditions) decreases hepatic steatosis and improves insulin sensitivity, however, there is concern that the rapid weight loss within the first few post-operative months may worsen liver disease progression[1,10].

Insulin Sensitizers

Small clinical trials involving treatment with metformin improved aminotransferase levels and reduced hepatic steatosis and fibrosis. However, in one study, though improvement was seen at 3 months, the difference was ameliorated at 12 months[28,29,30]. Pilot studies involving treatment with thiazolidinediones (pioglitazone and rosiglitazone) also showed improvement in aminotransferases, insulin resistance and liver histology. However, thiazolidinediones have potential adverse effects of cardiovascular complications, osteoporosis and weight gain with long term use[1,31].

Lipid Lowering Agents

There are concerns regarding the use of statins in individuals with chronic liver disease due to the potential for hepatotoxicity. Trials conducted using pravastatin and atorvastatin in NAFLD showed improvements in aminotransferases levels[31,32]. Another study involving patients who were treated with statins (simvastatin, atorvastatin, pravastatin) for a period of 10.3 to 16.3 years showed significant reduction in hepatic steatosis and reduced progression towards hepatic fibrosis[33]. Therefore, the conclusion was that statin use in stable NAFLD is safe, with hepatotoxicity being rare. Monitoring of transaminases should be carried out as per current guidelines[10,21,34].

Insufficient studies have been carried out using fibrates. Only one study was published involving Gemfibrozil treatment in patients with NASH, which showed biochemical improvement[35]. Ursodeoxycholic acid has not been shown to improve transaminases, hepatic steatosis on US or histology[36].

Angiotensin Receptor Blockers (ARBs)

Two pilot studies evaluating the effects of Losartan on NAFLD, showing improvement in transaminases, reduction in markers of hepatic fibrosis and improvement in histology[37,38]. A recent study comparing Telmisartan and Valsartan also showed improvement in transaminases, histology and insulin resistance indices. However, Telmisartan had a higher efficacy on histology changes and insulin resistance, possibly due to its additional effects on the PPAR-gamma ligand[39].

Anti-oxidants

A review of studies conducted on Vitamin E and its effects on NAFLD showed that Vitamin E increased transaminases and had no effect on hepatic radiological changes or histology[40].

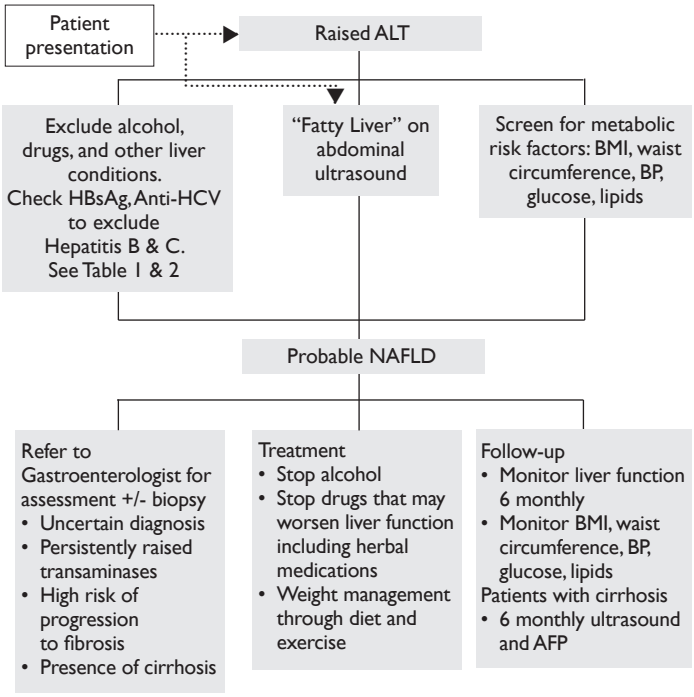
FOLLOW-UP

Follow-up of patients with NAFLD involves monitoring of liver function and metabolic risk factors. Liver function tests including ALT and AST are recommended 6 monthly. Though improvement in ALT could indicate resolution of hepatosis, it is also associated with progression to liver fibrosis, so it should be interpreted in the context of the patient's clinical condition. The recommendation of regular abdominal US for monitoring of NAFLD in the absence of cirrhosis is controversial as US does not provide information on the progression to NASH or fibrosis[7,9,21]. In patients with cirrhosis, regular 6 monthly screening for hepatocellular carcinoma with hepatobiliary US and alphafetoprotein (AFP) is recommended[41]. AFP has a sensitivity of 58% (15ng/ml) and specificity of 100% in detecting hepatocellular carcinoma in NAFLD patients[42]. Routine monitoring of cardiovascular risk factors include measurement of BMI, waist circumference, blood pressure (BP), glucose and lipid levels. Patients in whom the diagnosis is uncertain or who may require liver biopsy should be referred to a gastroenterologist for further assessment. Patients with suspected fibrosis or cirrhosis on abdominal US should also be referred.

CONCLUSION

Non-alcoholic fatty liver disease is a common disorder and will frequently require diagnosis by the family physician. Figure 1 outlines an approach to NAFLD for the family physician[43]. Patients should be carefully evaluated because NAFLD may progress to liver cirrhosis and hepatocellular carcinoma and is associated with increased cardiovascular deaths. Patients can be diagnosed based on presence of metabolic risk factors and US findings. However, those with persistently high transaminases, uncertain diagnoses and are at high risk of hepatic fibrosis should be referred for liver biopsy. Treatment currently consists of weight loss through diet and exercise. Though no pharmacological therapy has been approved for specific treatment of NAFLD, patients who require treatment for co-existing diabetes, hypertension and dyslipidaemia may benefit from the use of certain classes of drugs, also associated with progression to liver fibrosis, so it should be interpreted in the context of the patient's clinical condition.

Figure 1. Approach to NAFLD



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