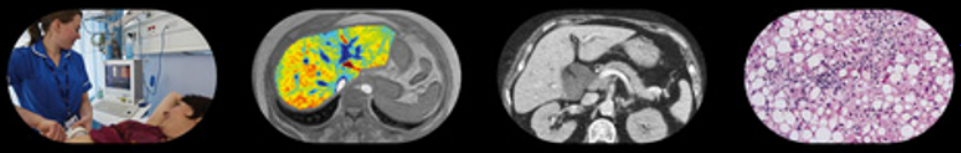

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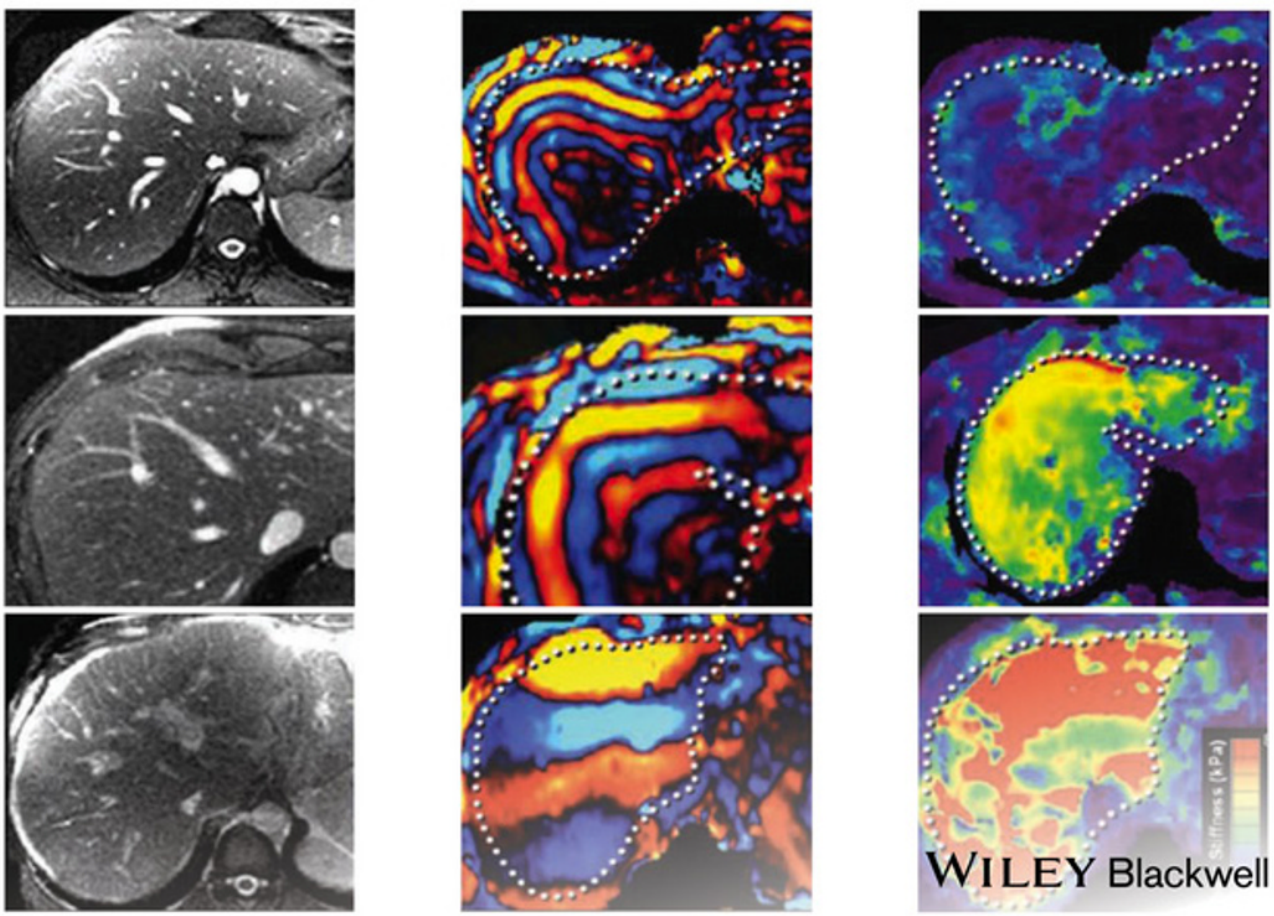

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Registered Office
John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data

Names: Williams, Roger, 1931–, editor. | Taylor-Robinson, Simon D., author.
Title: Clinical dilemmas in non-alcoholic fatty liver disease /
[edited by] Roger Williams, Simon Taylor-Robinson.
Description: Chichester, West Sussex ; Hoboken, NJ : John Wiley & Sons Inc., 2016. |
Includes bibliographical references and index.
Identifiers: LCCN 2015040510 | ISBN 9781118912034 (pbk.)
Subjects: | MESH: Non-alcoholic Fatty Liver Disease.
Classification: LCC RC848.F3 | NLM WI 700 | DDC 616.3/62–dc23
LC record available at http://lccn.loc.gov/2015040510

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 8.75/12pt Minion by SPi Global, Pondicherry, India

1 2016

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Preface

In this further volume in the Clinical Dilemmas series, we have attempted to provide for nonalcoholic fatty liver disease the latest and most critical information regarding the nature of the condition and the factors that lead to disease progression. How best to assess severity and value of currently available different treatment measures, including the role of bariatric surgery and its quite remarkable effects on diabetes, have separate sections. The final chapter is a look ahead—what does the future hold—and includes coverage of the new molecular targeted agents that are currently in preclinical and phase I clinical trial development.

With obesity constituting a worldwide epidemic with prevalent figures for NAFLD in some Western countries as high as 30–40% of the population, there are yet few signs of it being controlled by public health measures. Understanding the cross talk that underlies the involvement of a number of other organs and systems leading to cardiac and respiratory events and cancers of various organs is of critical importance. We hope that this volume will encourage the necessary investment in preventative, diagnostic, and treatment facilities needed if the effect of this lifestyle related and preventable condition on the health of many nations is to be reduced.

As editors we are grateful to the contributors worldwide who have made it possible with their expertise and commitment to produce what we believe is an outstanding volume. A personal thanks to Jasmine Chang, Project Editor; Jon Peacock, Senior Project Editor; Oliver Walter, Publisher at Wiley-Blackwell; and also to Enda O'Sullivan, Editorial Assistant in the Institute of Hepatology, London.

Professor Roger Williams, CBE
Professor Simon D. Taylor-Robinson

PART I
Nature of the Condition

1 Non-alcoholic fatty liver disease: Hype or harm?

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LEARNING POINTS

- Non-alcoholic fatty liver (NAFL) often presents the clinician with a conundrum in deciding the significance of the problem.
- It is now widely recognized that non-alcoholic steatohepatitis (NASH) can progress to advanced liver disease evident as cirrhosis with all of its attendant complications including portal hypertension and hepatocellular cancer, and sometimes this progression is associated with the perplexing loss of histological hallmarks of the antecedent process of steatohepatitis.
- The challenge to clinicians is to discern NASH from the relatively more stable forms of fatty liver, which we prefer to call non-NASH fatty liver (NNFL).
- Therapy of NASH is evolving and aside from common conservative measures like exercise and diet treatment is likely to involve drug therapy with potential side effects. Thus refining the prognosis and discerning harm from hype will be increasingly important.
- Additional areas of special need for further study include what is sometimes referred to as "BASH," which indicates the presence of metabolic risks such as obesity and insulin resistance and the use of ethanol above safe levels but below levels at which the risk of alcoholic steatohepatitis (ASH) rises steeply.

Few potentially fatal diseases have ever been referred to as "trash" in a serious and critical treatise on the topic [1] or have been specifically the subject of an unsuccessful legal action aimed at shutting down a particular form of animal-derived food production (Caldwell S, personal experience) or have at one time been, rather accurately, referred to as "big" and "little" varieties to indicate early recognized variability in severity from mild and essentially inconsequential to potentially fatal (McCullough AJ, personal communication). However, all of these attributes are true of non-alcoholic fatty liver disease (NAFLD) and its potentially more severe subset non-alcoholic steatohepatitis (NASH).

In many ways, NASH remains a very challenging disorder over 30 years after pathologist Jurgen Ludwig first coined the term "NASH" for a "hitherto unnamed" form of steatohepatitis [2], and in doing so, he and his colleagues ushered in the modern era of clinical and basic research into the various forms of nonalcohol-related fatty liver—a field that has grown from a few published papers per year to many publications per week or month. On a practical level, much of the persistent challenge hinges on questions about the natural history and prognosis of fatty liver when it is encountered in a given individual—currently an almost daily occurrence in many clinics whether on its own or in combination with other liver disorders. The patient usually presents with asymptomatic, mild to moderate range of abnormal liver enzymes, negative additional diagnostic testing, and fatty changes noted on diagnostic ultrasound. This raises a frequent clinical question: is fatty liver a benign physiological finding (possibly an ancient adaptation to feast or famine, where nowadays feast exceeds famine), is it a disease warranting liver biopsy (with inherent risk) and directed intervention, or is it an epiphenomenon of a metabolic disorder encompassing diabetes mellitus, vascular disease, and cancer risks with clinical consequences that supersede the significance of the fatty liver [3]? All of these posits have some truth in NAFLD/NASH

Clinical Dilemmas in Non-Alcoholic Fatty Liver Disease, First Edition. Edited by Roger Williams and Simon D. Taylor-Robinson.

and constitute the pressing clinical challenge to discern hype and harm.

"Big" NASH and "little" NASH are now somewhat forgotten terms used casually in the discussion of early natural history studies, which indicated a dichotomy in the clinical course: long-term stability of the liver in many patients and progression to cirrhosis and liver-related mortality in a smaller but substantial fraction [4]. Since those early days, the nomenclature has obviously evolved with recognition of potentially progressive "big" NASH, characterized by cellular injury and fibrosis, as a subset of the more global term, NAFLD, which indicates liver fat exceeding 5–10% triglyceride by weight. Subsequently, long-term natural history studies of NAFLD have consistently demonstrated this dichotomous natural history: non-NASH fatty liver tends to be stable over years with low liver-related mortality, while NASH carries a significant, tangible risk of progression to cirrhosis and associated liver-related mortality [5–8]. Most of these studies have focused on mortality rather than morbidity, and overall mortality is clearly dominated by cardiovascular disease and nonliver malignancy. These findings suggest that the emphasis on the liver disease itself may be somewhat misplaced. However, this overlooks the fact that a substantial number of patients, especially those with histological NASH will progress to cirrhosis and suffer many of the typical cirrhosis-related complications. Moreover, the development of cirrhosis and coexisting vascular disease or neoplasm significantly complicates the management of either condition. Thus, directing specific therapy at the liver is appropriate in some patients, but careful patient selection is essential, and unless a therapy is very safe and inexpensive (such as diet and exercise), many NAFLD patients warrant only conservative management. Riskier interventions should be directed at those with histological NASH especially with more advanced fibrosis stages.

Is steatosis ever physiologically adaptive? To some extent it can be viewed as such under certain circumstances [9]. This is most evident in certain species of migratory *Palmipedes* spp. (geese and ducks) where the development of steatosis is a normal premigratory process and presumably provides a source of energy during the long flight with little calorie intake. This process was recognized long ago, and for thousands of years, "foie gras" production has hinged on it. However, our own work in cooperation with several individuals in France demonstrated that the *Palmipedes* develop only non-NASH fatty liver. Hence, the effort by People for the Ethical Treatment of Animals (PETA) to block foie gras production in the United States—on the grounds that the meat represented a disease state—failed due to the absence of NASH. No doubt, the grounds for the attempted legal action were the result of some of the media publicity that has surrounded NAFLD.

On the other hand, humans with histological NASH are at risk for progression of fibrosis through stages to cirrhosis. Serial biopsy studies suggest that this is a slow, steady march when it occurs [10]. However, it remains unclear whether or not the progression is uniform over time, and it is conceivable that NASH progression may occur in subclinical "fits and starts" with peaks and troughs of disease activity rather than by a slow, steady process. It has also been shown that some patients with non-NASH fatty liver may transition to histological NASH [11]. Presumably, changes in activity, diet, or weight with resultant worsening insulin resistance may trigger such a transition. Once cirrhosis develops in patients with NASH, complications of portal hypertension develop at a steady rate but somewhat slower than that seen with cirrhosis due to hepatitis C [12]. Patients are also at significantly increased risk of hepatocellular cancer usually, but perhaps not always, in the setting of coexisting cirrhosis [13].

Adding to the clinical diagnostic challenge, when cirrhosis develops in NASH, steatosis, a hallmark of NASH, tends to diminish significantly, sometimes leaving a picture of "cryptogenic cirrhosis," especially in patients without a confirmed antecedent diagnosis of NASH [14–16]. Such patients often present with minor findings, such as asymptomatic and previously unexplained thrombocytopenia, often labeled in prior encounters as idiopathic thrombocytopenia purpura ("ITP") or with cirrhosis, incidentally discovered at the time of elective surgery, especially for suspected or confirmed gallbladder disease. The mechanisms underlying diminished liver fat remain uncertain but may involve altered insulin exposure through changes in blood flow or repopulation of the liver from stem cells with altered physiology and fat metabolic capacity. Clearly, there are also other causes of cryptogenic cirrhosis, including silent autoimmune hepatitis, occult ethanol abuse, or as yet unrecognized viral infection, but NASH appears to be the leading etiology in many areas of the world [17].

Although it is well established that NAFLD has a largely dichotomous natural history, based on initial histology (NASH vs. non-NASH fatty liver), it is perplexing that certain aspects of NASH histology remain challenging.

While there are a number of characteristic histological findings, the key features that usually are used to define NASH are steatosis, inflammation, cellular ballooning, and fibrosis; the first three of these parameters define the commonly utilized NAFLD activity score (NAS) [18, 19]. Perhaps not surprisingly, histological fibrosis appears to be a reliable finding with low interobserver variation rates and a reliable indicator of prognosis. However, agreement between scoring systems and individual parameters remains a potentially significant problem that can muddy clinical trials and natural history studies [20–22]. Defining criteria for cellular ballooning has been especially problematic although emergence of keratin staining as a means of characterizing pathological processes within these cells may lead to beneficial refinements of histological criteria [23–26].

ASH, NASH, BASH (indicating both alcohol exposure and risks for metabolic fatty liver), chemical-associated steatohepatitis (CASH), and drug-associated steatohepatitis (DASH): the nomenclature for the recognized varieties of steatohepatitis has continued to evolve over the years [27]. While by no means uniformly accepted, the term "BASH" ("B" for both alcohol and metabolic fatty liver) denotes possibly the most significant of these, as it indicates the presence of metabolic risks for NASH such as obesity, diabetes, and inactivity together with ethanol use above safe levels but below levels at which the risk of ASH rises steeply [28]. This represents a potentially important gray area, and it highlights the fact that the diagnosis of "NASH" is truly both a clinical- and pathology-based exercises that is not always clear cut [29, 30].

What about the individual patient who is seen in the clinic and presents with the "chief complaint" of abnormal liver enzymes, negative additional testing, and fatty changes on diagnostic ultrasound? Is it a benign finding, a marker for comorbid vascular disease and cancer risk, or a disease warranting liver biopsy and more aggressive therapeutic management recommendations than diet and exercise? Recent advances in genetic risks promise to further help sort hype from harm in NAFLD. PNPLA3 and TM6SF2 polymorphisms code for gene products that appear to be intimately involved with small fat droplet and lipoprotein metabolism and impart significant risk for steatosis and related organ injury [31–34]. Although far from being available as clinical tools, this work points out the continued clinical importance of the family history in NASH/NAFLD [35]. Indeed, we recommend earlier consideration of biopsy when, as often is the case, a family member is significantly affected even if the relative was reported to have had alcohol-related liver disease. Moreover, preliminary work from our group suggests that PNPLA3 polymorphism may predict response to such mild agents as omega-3 fatty acid supplements.

Clearly, NASH progresses to advanced stages of fibrosis, cirrhosis, and hepatocellular cancer reasonably often, and it may shed some its histological hallmarks in the process, which can complicate the diagnosis. Recognition of this phenomenon has allowed clinicians to avoid Dr. Ludwig's "embarrassment" in diligently attempting to ferret out the occult alcoholic when actually confronted with frank NASH. Without doubt, the emergence of this field coexists with a degree of hype, which has likely been magnified due to the parallel obesity epidemic. It is all the more important to sort out, within the limitations of existing literature, the hype from the harm in order to best tailor emerging pharmacological treatment strategies and match risks and benefits.

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2 NAFLD: A worldwide problem

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LEARNING POINTS

- The prevalence of worldwide obesity has nearly doubled since 1980, now exceeding 50% in some regions. Obesity prevalence has also increased in children, with ~23% of children in developed countries and 13% of children in developing countries now either overweight or obese.
- The close association between obesity and non-alcoholic fatty liver disease (NAFLD) has resulted in this now representing the most common cause of liver disease in Western countries, where it affects 20–30% of the adult population.
- Prevalence of NAFLD in countries such as Asia, Latin America and the Caribbean has risen as a result of increasingly urban and westernised lifestyles.
- The lowest estimates of NAFLD prevalence in Asia are from rural areas inhabited by more physically active, less affluent and lean populations.
- Estimates from biopsy series indicate an overall prevalence of the more advanced form of NASH of 3–5% in the United States, rising to 12% in some populations.
- In Europe and the United States, NAFLD is usually associated with obesity and insulin resistance. However in Asian countries the disease can manifest at a lower BMI; therefore application of ethnic-specific BMI thresholds is important to ensure accurate identification of higher-risk individuals.
- The incidence of NASH-related HCC is rapidly increasing, with NASH now the second leading aetiology of HCC-related liver transplantation in the United States and an increasingly frequent cause of HCC in Asia.
- Significant ethnic variations in propensity to NAFLD exist, which are largely accounted for by genetic factors. The extensively validated genetic modifier of NAFLD is the PNPLA3 polymorphism, which increases propensity to NAFLD, severity of disease and risk of HCC.
- NAFLD frequently acts as a cofactor with viral hepatitis, alcohol and other liver diseases to increase severity of liver injury.

Introduction

NAFLD is a complication of over-nutrition, being closely associated with obesity, diabetes and insulin resistance (IR), dyslipidaemia and hypertension. It is therefore recognised to represent the hepatic manifestation of the metabolic syndrome. The increasing global levels of obesity, IR and metabolic syndrome, driven by the trend of post-industrialised countries towards urban and inactive lifestyles, with easy access to cheap processed foods, have led to an estimated 20-fold increase in the prevalence of NAFLD since 1983 [1]. NAFLD now represents the most common cause of abnormal liver tests and chronic liver disease in the Western world [2–4] and is projected to become the leading cause of cirrhosis and most common indication for liver transplantation in the United States by 2030 [5]. More recent data demonstrate that the trend towards more urban and Westernised lifestyles occurring in many countries, which until the last few decades have been less well-developed, has resulted in NAFLD

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now playing an equally important role in Asia, Latin America and the Caribbean, establishing it as a truly global disease.

Although NAFLD is highly prevalent worldwide, the epidemiology and demographic characteristics vary in different populations. In Europe and the United States, NAFLD is associated with obesity and IR in the great majority of cases; however in Asian countries the disease can manifest at a lower BMI, albeit most often after a period of weight gain and with central adiposity. NAFLD also frequently acts as a cofactor with other liver diseases, and its impact is therefore influenced by the prevalence of other injurious factors such as viral hepatitis and alcohol consumption in different populations.

Prevalence of NAFLD worldwide

A variety of methodologies have been used to study the prevalence of NAFLD in different populations (Table 2.1). Although histology provides the most definitive data, liver biopsy is invasive and not amenable to population studies. The most commonly used diagnostic modalities for such studies have been ultrasonography and/or elevations in liver transaminase levels, although data has also been obtained from autopsy studies and MRI imaging.

Europe

Two large ultrasound-based studies in Italian and Spanish populations indicate a prevalence of NAFLD of between 20 and 30% in Europe. The Dionysos nutrition and liver study demonstrated the prevalence of NAFLD in a general Italian population to be 25 and 20% in subjects with and without suspected liver disease, respectively [6]. A Spanish multicentre population study demonstrated a prevalence of NAFLD of 33% in men and 20% in women [7].

TABLE 2.1 Estimated prevalence of NAFLD in different geographical regions

Region	Estimated prevalence (%)
United States	20–46
Europe	20–30
South/South East Asia	5–32
East Asia	11–45
Australasia	20–30

United States

A large multi-ethnic, population-based study of 2287 individuals using proton magnetic resonance spectroscopy (MRS) to measure intrahepatic triglyceride content demonstrated NAFLD to be present in approximately one third of American adults [8]. A higher ultrasonographic NAFLD prevalence of 46% was demonstrated in a study of over 300 middle-aged patients performed at the Brooke Army Medical Center. In this study, 30% of those with NAFLD were confirmed by liver biopsy to have NASH [9]. Importantly, these figures mask significant ethnic variations in disease prevalence, with significantly higher rates in Hispanics > white populations > African Americans [8, 9]. The lower frequency of hepatic steatosis in blacks is not explained by ethnic differences in BMI or IR [8] and is fully accounted for by genetic factors (see later). Such studies, and the >30% obesity prevalence in the adult population, suggest an estimated NAFLD prevalence in the United States of at least 30%.

Although there are limited data from Latin America, the prevalence of NAFLD in this area has been reported to range between 17 and 35% [10]. A 2007 study reported an ultrasonographic NAFLD prevalence of 35% in community-dwelling middle-aged and older adults in Brazil, a high proportion of whom had metabolic syndrome [11]. The population prevalence of NAFLD in Mexico is estimated at 20–30%, based on an approximate 30% prevalence of obesity [12], with steatosis demonstrated in 83% of a cohort of 198 Mexican subjects with metabolic syndrome [13].

Asia

NAFLD was originally regarded as a disease of highly industrialised Western nations, occurring as a consequence of increasingly sedentary behaviour with abundant availability of energy-dense foods. However, the major lifestyle and dietary changes observed in many Asian countries in recent decades, resulting from increased urbanisation and industrialisation, have led to a marked increase in the prevalence of NAFLD, with recent studies reporting levels similar to those in Europe and the United States [1, 14]. Further, genetic predisposition to type 2 diabetes is higher in many Asian populations, and such predisposition is very relevant to both the prevalence and severity of NAFLD [15–17]. Prevalence of NAFLD in Japan increased from 13% in 1989 to 30% by 1998 and ~32% in men and 17% in women by 2008 [18]. This rise was associated with a significant

increase in fat intake and number of registered motor vehicles, increasing urbanisation and GDP, increased import of soft drinks and processed foods from outside Asia, and increasing availability and consumption of fast food [1, 18]. A similarly high NAFLD prevalence of 11–45% has been reported in Korea, China and Taiwan [1, 19–21].

The prevalence of NAFLD in South and South East Asian countries has been reported to range from 5 to 32% [1, 22–25]. A population-based study in a rural south Indian community demonstrated a NAFLD prevalence of 32%, based on ultrasound and measurement of metabolic risk factors [24].

The lowest estimates of NAFLD prevalence in Asia are from rural areas inhabited by more physically active, less affluent and lean populations. A large study of >11 000 residents of Indian railway colonies demonstrated an overall prevalence of ultrasonographic NAFLD of 17%, and 19% in individuals over 20 years [26], with a prevalence of only 8.7% in a large study in a rural community in West Bengal [22].

Australasia and Pacific Islands

The prevalence of NAFLD in Australia and New Zealand is reported to be similar to Northern Europe at between 20 and 30% [27]. Although there are few data from the Pacific Islands, the strikingly high prevalence of obesity and diabetes, which exceeds 50% in several populations including Tonga, Nauru, Federated States of Micronesia, Tonga and Samoa [28], predicts a high burden of NAFLD in these areas.

Africa

A paucity of data exists on the prevalence of NAFLD in Africa, and further research is required in this area. One study reported a NAFLD prevalence of ~9% in Nigeria [29], but it is likely that similar differences between rural and urban areas to those observed in Asia will exist here. Given the high prevalence of fatty liver and diabetes associated with hepatitis C in Egypt (see later), it may be that NAFLD is also common in Egypt, but this requires further study.

Disease severity

NAFLD encompasses a pathological spectrum of disease ranging from simple steatosis through steatohepatitis (NASH), characterised by lobular inflammation and hepatocyte ballooning, with increasing fibrosis to eventual cirrhosis with risk of hepatocellular carcinoma (HCC). Studies with up to 20 years follow-up have demonstrated that simple steatosis is usually associated with a relatively benign prognosis, whereas the diagnosis of NASH, particularly with the presence of fibrosis, is associated with increased liver- and cardiovascular-related morbidity and mortality [30, 31].

Despite many advances in the non-invasive assessment of NAFLD, liver biopsy is still required to make a definitive diagnosis of NASH. This precludes large population assessments of NASH prevalence, but recent smaller studies have shown a high prevalence of NASH among NAFLD cases ranging from 10 to 25%. Estimates from biopsy series indicate an overall prevalence of NASH of 3–5% in the United States, although in some populations this may be as high as 12% [9]. In European and US studies, histological NASH was present in up to 30% of patients with ultrasound-detected steatosis [9], in 20–33% of patients with elevated aminotransferases [32, 33], in 32–37% in morbidly obese patients [34, 35] and in 3–16% in apparently healthy, living liver donors [36, 37]. Data on the prevalence of NASH in Asian and African patients with NAFLD are lacking and represent an area requiring further study.

NAFLD-related cirrhosis is now the third most common indication for liver transplantation in the United States and is projected to overtake alcoholic liver disease and HCV as the leading indication in future decades. As cirrhosis usually takes several decades to develop, the prevalence of advanced disease is currently less common in Asian countries where the rise in NAFLD prevalence has been more recent. However, this is expected to increase in future decades as the current cohort ages, and as a result of the increasing prevalence of NAFLD in children and young people [1]. The incidence of HCC secondary to NASH is also increasing, with NASH now the second leading aetiology of HCC-related liver transplantation in the United States [5]. A notable increase in NAFLD-associated HCC has also been observed in Asia. A study of 329 patients in South Korea reported an increase in the proportion of cases of HCC associated with NAFLD from 3.8% in 2001–2005 to 12.2% in 2006–2010, at the same time as a decrease in HBV-attributable HCC [38], and NAFLD now accounts for 2% of HCC in Japan [1, 18, 39]. Although the estimated 2–3%/year risk of incident HCC in NASH is lower than in cirrhosis associated with HBV or HCV, the much greater number of patients with NASH renders the absolute

burden of NASH-related HCC higher. While HCC most commonly occurs in the presence of cirrhosis, it is also increasingly observed in non-cirrhotic NASH [40, 41]. If confirmed by prospective studies with careful histological assessment, this finding has considerable implications for both screening and future disease burdens.

Obesity and metabolic syndrome

Obesity

Obesity is closely associated with NAFLD, and increased BMI is a risk factor for liver disease progression. The prevalence of worldwide obesity has nearly doubled since 1980, with more than 1.4 billion adults overweight and over 200 million men and nearly 300 million women obese worldwide by 2008 [42]. A recent systematic analysis of the worldwide changes in the prevalence of overweight and obesity reported that the global proportion of adults with a body mass index (BMI) of 25 kg/m^2 or greater increased from 28.8 to 36.9% in men and from 29.8 to 38.0% in women between 1980 and 2013 [28]. Estimated prevalence of obesity exceeded 50% in some regions, including several Pacific Islands, Kuwait, Libya and Qatar. Prevalence has also increased markedly in children and adolescents, with approximately 23% of children in developed countries and 13% of children in developing countries overweight or obese in 2013. Concerningly, despite the major global health challenge posed by obesity, no national success stories in addressing the issue have been reported in the past 33 years [28]. Unless unprecedented progress is made in reversing this trend, it is therefore expected that the prevalence of NAFLD and its complications will continue to proliferate worldwide.

Metabolic syndrome

South and East Asians appear to be at increased risk of NAFLD, IR, type 2 diabetes and metabolic syndrome, and tend to develop these features at a lower BMI than in other ethnic groups. For a given BMI, both the percentage of fat and its distribution between the subcutaneous and visceral depots differ between European and South and East Asian people [1]. This ethnic difference in susceptibility to IR and metabolic syndrome accounts for the oft-cited observation that NAFLD is more common in 'lean' South and East Asians than individuals from other ethnic groups, and the term 'metabolically obese' has been given to such lean, but insulin resistant, individuals. The finding that IR, diabetes and NAFLD occur at a lower BMI in South and East Asians has led to revision of the BMI thresholds for obesity in Asian people [43], and in fact only ~15% of Asians with NAFLD would be classified as lean using ethnic-specific anthropometric indices [1, 22, 44, 45]. Greater awareness and application of ethnic-specific BMI thresholds are essential to ensure accurate identification of higher-risk individuals.

Genetic predisposition

Genetic studies, including several large genome-wide association studies (GWAS), have identified an increasing number of genetic single nucleotide polymorphisms (SNPs), which may be associated with increased risk of NAFLD and/or disease severity in different populations. To date, the most extensively investigated and validated genetic modifier of NAFLD is polymorphism in the adiponutrin or *PNPLA3* gene. In multiple studies, PNPLA3 variants have been shown to increase both prevalence and severity of NASH and, more recently, risk of HCC (in both NASH and alcoholic liver diseases) [46]. In one large GWAS study, this polymorphism was shown to fully account for the ethnic differences in prevalence of NAFLD between Hispanics, white populations and African Americans living in the United States [47].

Several other genetic polymorphisms have been identified, which may also contribute to ethnic differences in susceptibility to NAFLD. A GWAS study in a US population reported a strong association between NAFLD and the farnesyl-diphosphate farnesyltransferase 1 (FDFT1) genotype in non-Hispanic women [48]. Other SNPs associated with NAFLD include Kruppel-like factor 6 (KLF6) [49], PPARα [50], PPARγ [51] and APOC3 (the findings here are not consistent) [52], all of which play important roles in the regulation of insulin sensitivity and/or lipid metabolism. Ongoing research will undoubtedly identify more genetic modifiers and add to our understanding of individual and population differences in susceptibility to NAFLD, possibly facilitating identification of individuals at higher risk and potentially informing the development of novel therapies.

NAFLD as a cofactor

NAFLD and the metabolic syndrome can also act as a cofactor with other liver diseases to enhance disease progression. This is of particular importance in many Asian countries with a high prevalence of viral hepatitis. Areas of highest hepatitis B prevalence include South East Asia, China,

sub-Saharan Africa and the Amazon basin, where at least 8% of individuals are HBV carriers [53]. Although steatosis is less common in Asian patients with HBV than the general population, when present it is usually associated with the same metabolic factors as NAFLD [54–56], and the risk of cirrhosis is significantly higher in individuals with both hepatitis B and metabolic syndrome than in lean subjects with hepatitis B [57]. Further, HBV-infected patients with metabolic syndrome are more likely to have cirrhosis than those without [58], indicating interactions between fatty liver and hepatitis B can worsen disease progression.

Prevalence of hepatitis C is highest (>3.5%) in Central and East Asia and North Africa/Middle East, with moderate prevalence (1.5–3.5%) in South and South East Asia, sub-Saharan Africa, Latin America, Caribbean, Australasia and Europe [59]. The effects of fatty liver, obesity and diabetes on liver disease with chronic HCV infection include more rapid progression to cirrhosis, higher incidence of HCC and suboptimal response to interferon-based therapy. Further, chronic HCV infection increases incidence of type 2 diabetes several fold, and is associated with increased all-cause mortality largely attributable to cardiovascular and liver disease [60]. It is therefore predicted that coincidence of NAFLD with HCV will significantly increase the burden of chronic liver disease and HCC in future.

NAFLD can also exacerbate damage caused by other liver diseases, including haemochromatosis and alcoholic liver disease [55], whose prevalence also varies in different geographical regions.

Conclusions

The incidence and prevalence of NAFLD is increasing worldwide as a consequence of the rising levels of obesity and metabolic syndrome. Recognition of the global importance of NAFLD and its complications of portal hypertension, liver failure and HCC, is reflected in the development of practice guidelines by Medical Societies encompassing all continents, including both the American [4] and European [61] Associations for the Study of Liver Disease, the Asia-Pacific Working Party for NAFLD [62], World Gastroenterological Association [63] and the Chinese Liver Disease Association [19]. NAFLD is more prevalent in certain ethnic groups, and identification of several genetic polymorphisms has helped to increase our understanding of these differences in susceptibility. The precise pathogenetic mechanisms underpinning the development and progression of NAFLD are not yet fully understood and likely vary in different populations due to complex interactions between genetics, diet, hepatic lipid handling, microbiome and environmental influences [64].

Effective treatments for NAFLD are currently lacking, with existing treatment strategies primarily directed towards lifestyle modification and control of metabolic risk factors. Ongoing research into ethnic and genetic differences in susceptibility could help to further our knowledge of the pathogenesis of NAFLD and should inform the development of novel therapeutic strategies. There is a need for further longitudinal studies to delineate the natural history of the condition in different ethnic groups and to more accurately chart the changing prevalence in developing countries. The advances in non-invasive methods to diagnose and stage NAFLD without recourse to liver biopsy should facilitate such studies in the future. However, the most urgent priority remains reversal of the inexorable global trend of rising obesity levels, sedentariness and unhealthy eating behaviours, which underpin the burgeoning NAFLD epidemic. This will require education and public health interventions at both the individual and population levels.

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3 Is insulin resistance the principal cause of NAFLD?

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LEARNING POINTS

- Conditions where insulin resistance is a feature (e.g. obesity) are associated with a high prevalence of NAFLD.
- Insulin resistance is conventionally measured in terms of glucoregulatory insulin resistance, but antilipolytic insulin resistance may be more important with regard to fatty liver.
- Antilipolytic insulin resistance has mostly been evaluated in terms of the ability of plasma insulin to lower plasma non-esterified fatty acid (NEFA) or glycerol levels, although an agreed reference method has yet to be established.
- *De novo* lipogenesis in the liver is stimulated by the hyperinsulinaemia of insulin resistance, but most hepatic triglyceride derives from circulating NEFA of adipose tissue origin.
- Insulin stimulates fatty acid uptake into the liver, *de novo* lipogenesis and hepatic triglyceride synthesis, and it inhibits fatty acid oxidation and hepatic VLDL secretion. Accordingly, the hyperinsulinaemia of insulin resistance promotes hepatic fatty accumulation.
- Although hepatic steatosis may occur in the absence of insulin resistance, insulin resistance does appear to be an important pathogenetic factor. However, the importance of hepatic insulin resistance may have been exaggerated since hepatic steatosis appears to be largely a consequence of adipose tissue NEFA release.

Introduction

A relationship between insulin resistance and non-alcoholic fatty liver disease (NAFLD) has been recognised for many years, but whether insulin resistance is an aetiological factor in NAFLD or simply an accompanying feature continues to be debated. In this chapter, we review some of the evidence. We begin with a brief examination of the mechanisms of insulin resistance and how insulin sensitivity is measured with particular emphasis on insulin resistance as it relates to lipid metabolism. Some of the clinical situations where insulin resistance and NAFLD coexist are reviewed. Potential aetiological mechanisms for NAFLD are discussed and potential causative links between insulin resistance and NAFLD are examined.

Clinical Dilemmas in Non-Alcoholic Fatty Liver Disease, First Edition. Edited by Roger Williams and Simon D. Taylor-Robinson.