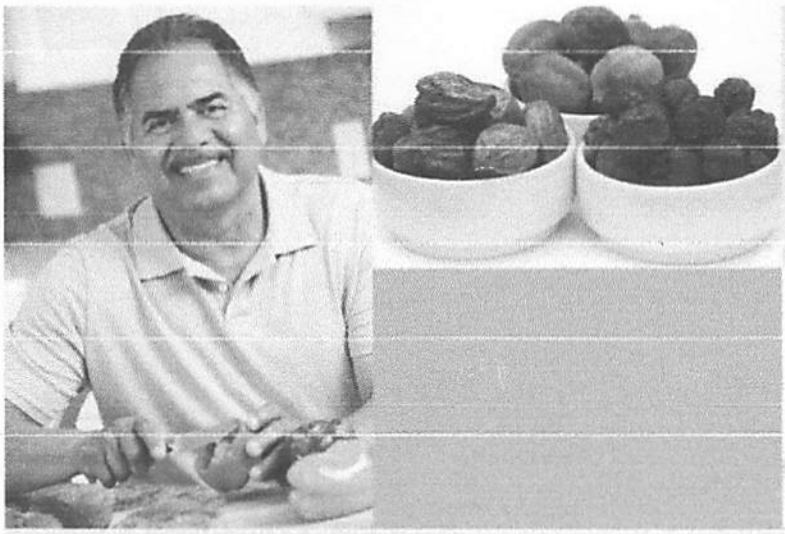
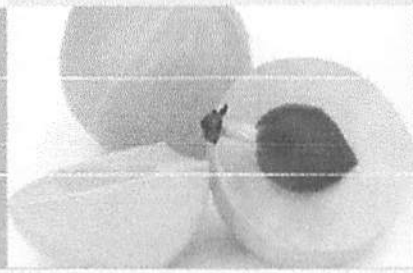

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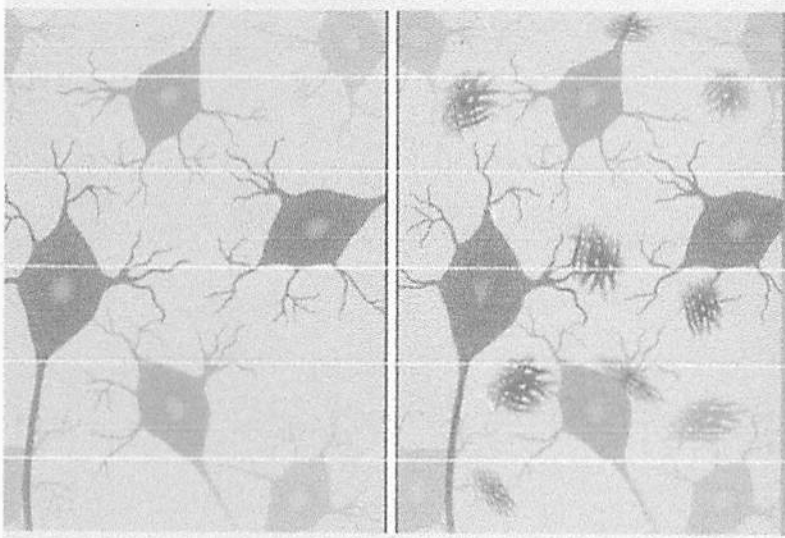


Edited by

Ronald Ross Watson


FOODS AND DIETARY SUPPLEMENTS IN THE PREVENTION AND TREATMENT OF DISEASE IN OLDER ADULTS

Edited by

RONALD ROSS WATSON

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The Progression of Non-alcoholic Fatty Liver Disease and Lifestyle Intervention in Older Adults

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9.1 INTRODUCTION

The term "non-alcoholic fatty liver disease" (NAFLD) describes a spectrum of liver histology characterized by excess fat within the liver in individuals who drink little or no alcohol. It ranges from simple fatty liver (steatosis), through fat accompanied by signs of hepatocyte injury, mixed inflammatory cell infiltrate, and variable hepatic fibrosis (non-alcoholic steatohepatitis, NASH), to cirrhosis and hepatocellular carcinoma (HCC) [1,2]. The histological characteristics of NAFLD are indistinguishable from alcoholic liver disease; however, excluding patients with a history of excessive alcohol use is critical in defining who has NAFLD [1,3]. NAFLD has become a common reason for liver transplant. It also has been identified as an important risk factor for the development of primary liver cancer, mostly due to NAFLD-associated cirrhosis [1–3].

Understanding the burden of NASH in the NAFLD population is important because whereas hepatic steatosis alone is considered to be relatively benign from a liver perspective, with a 0–3% liver-related mortality rate over 10–20 years, NASH presence has been associated with a 17.5% risk of liver-related mortality over approximately 20 years of follow-up in a series of 131 subjects [4,5]. A significant minority of people with simple steatosis will also develop NASH over time, as illustrated by one comprehensive follow-up series using serial liver biopsy, where 23% of patients with simple steatosis were found to progress to NASH in a period of 3 years [6].

9.2 PREVALENCE OF NAFLD AND NASH

NAFLD is rapidly becoming a global public health problem. It is the most common liver disease in the United States, and indeed worldwide. Current estimates are that about 19.0% of the general population of the United States had NAFLD detected by hepatic ultrasonography [7,8], and that around 11.8% of NAFLD patients developed NASH [8]. The prevalence of NAFLD among adults in the general population in China was found to be approximately 15.0% [9]. NAFLD was found in over one-quarter of the general adult Chinese population in Hong Kong, but the proportion of patients with advanced fibrosis was low (3.7%) [10]. NAFLD was highly prevalent (29.7%) in the general population in Japan in 2009–2010, and the estimated prevalence of NASH was less than 10.0% in subjects with NAFLD [11]. Additionally, the prospective definition of the prevalence of NAFLD and NASH was higher than estimated previously: NAFLD and NASH affected as many as 46.0% and 12.2% of United States middle-aged adults, respectively;

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CHAPTER

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Those with liver complications are more often in their sixth through eighth decades of life [42,43]. This could be related to the increasing rate of fibrotic progression with age [37], or to mitochondrial dysfunction (which causes steatosis and hepatic insulin resistance) developing in the elderly [44]. Concerning cirrhotic NASH patients, the prevalence in women was higher than that in men (57% in women and 43% in men) [45]. In contrast, the prevalence of hepatocellular carcinoma was higher in men (38% in women vs 62% in men) [46]. This gender difference may be attributable to differences in exposure to risk factors for HCC, such as cigarette smoking. However, it was recently reported that estrogen-mediated inhibition of IL-6 production in mice models explains the gender disparity in the development of HCC [47]. Estrogen may play a role in the pathogenesis of HCC. Further studies are needed to clarify the pathogenesis of gender differences.

9.3.3 Genetics

A number of studies over the years have revealed a genetic predisposition to NAFLD. As data have accumulated, it has become clear that ethnic differences play a role in susceptibility to NAFLD, especially progressive NAFLD, which cannot be explained simply on the basis of diet or socioeconomic differences. Recent reports of the Third National Health and Nutrition Examination Survey [7], conducted in the United States from 1988 to 1994, found a more common incidence of NAFLD in Mexican Americans (24.1%) compared with non-Hispanic whites (17.8%) and non-Hispanic blacks (13.5%) ($P = 0.001$). A prospective study newly reported that Hispanics had the highest prevalence of NAFLD (58.3%), followed by Caucasian (44.4%) and African Americans (35.1%), in a middle-aged United States population [12]. Because of the mixed racial heritage of such populations in the United States, it would be useful in the future to identify them more precisely using accepted racial-origin genetic markers. This is of particular importance when accumulating data that may ultimately be used to set public policy regarding population screening and/or public health intervention strategies.

Several case studies of familial clustering of NAFLD and NASH have been reported [48], further suggesting that genetic factors may play a role in the pathogenesis of NAFLD. Recently, samples from populations with well-defined NAFLD have begun to be used for genome scans to pinpoint gene variants that are more common in NAFLD patients than in control populations. Romeo *et al.* [49] reported that genetic variation in PNPLA3 confers susceptibility to NAFLD. Other groups have examined single nucleotide polymorphism variants in candidate genes chosen for their known implication in the regulation of lipid metabolism, or their relationship with risk factors for NAFLD [50–52]. In addition, gene/environment interactions are increasingly being explored, and studies have begun to look for chromosomal regions harboring gene variants that affect the onset of NAFLD and its progression [2].

9.3.4 Lifestyle

Non-alcoholic steatohepatitis has been referred to as a disease of the West, in which altered socioeconomic circumstances and related changes in food intake, food composition, and physical activity (together referred to as "lifestyle") may each play a role [1]. Poor dietary habits have been implicated in the development of NAFLD; however, little is known about the role of specific dietary patterns in its development. Oddy *et al.* [53] examined prospective associations between dietary patterns and NAFLD in a population-based cohort of adolescents, and found that NAFLD was present in 15.2% of them. A higher Western dietary pattern score at 14 years was associated with a greater risk of NAFLD at 17 years (OR 1.59, $P < 0.005$), although these associations were no longer significant after adjusting for BMI at 14 years. However, a healthy dietary pattern at 14 years appeared to be protective against NAFLD at 17 years in centrally obese adolescents (OR 0.63, $P = 0.033$), whereas a Western dietary pattern was associated with an increased risk of NAFLD [53]. Nutritional assessments showed that NAFLD patients consumed low-nutrient food, more high-sodium food, more high-fat sources of meat/protein, and few calories from fruits [54].

A cross-sectional study investigated dietary patterns associated with primary NAFLD, and found that the NAFLD group consumed almost twice the amount of soft drinks ($P = 0.030$) and 27% more meat ($P < 0.001$) [55]. In contrast, the NAFLD group consumed somewhat less fish rich in omega-3 ($P = 0.056$). Moreover, a higher intake of soft drinks and meat was significantly associated with an increased risk for NAFLD, independent of age, gender, BMI, and total calories [55]. It has been noted that soft drinks are the leading source of artificially added sugar in the world, and have been linked to obesity in children and adolescents [56]. Recent evidence suggests an association between the intake of sugar-sweetened soft drinks and the risk of obesity and diabetes, because the drinks contain large amounts of high-fructose corn syrup, which raises triglycerides and blood glucose similarly to sucrose [56,57]. Individuals consuming more than one soft drink daily showed a higher prevalence of MetS than those consuming less than one soft drink per day [57]. It has been reported that soft drink consumption is a strong predictor of NAFLD independent of a MetS diagnosis [58]. In that study, 80% of patients with NAFLD had excessive intake of soft drinks (>500 cm^3/day) compared to 17% of healthy controls ($P < 0.001$). The NAFLD

group consumed five times more carbohydrates from soft drinks compared to healthy controls (40% vs 8%, $P < 0.001$). Of these patients, 7% consumed one soft drink per day, 55% consumed two or three soft drinks per day, and 38% consumed more than four soft drinks per day on most days, and for the whole study period [58]. Indeed, dietary fructose consumption by NAFLD patients was excessive, nearly two- to three-fold higher than in controls [59]. Furthermore, hepatic metabolism of fructose favors *de novo* lipogenesis and adenosine triphosphate depletion, which contribute to the development of NAFLD [59]. An additional study found a significant association between higher carbohydrate intake in NAFLD patients and liver inflammation [60].

A study of dietary habits revealed that dietary intake of NASH patients was high in saturated fat and cholesterol, but low in polyunsaturated fat, fiber, and antioxidant vitamins C and E, in comparison with healthy controls. Saturated fat intake correlated with the insulin sensitivity index, the different features of MetS, and the postprandial rise of triglycerides [61]. Here, it is of importance to understand that dietary cholesterol is an important risk factor for the progression of steatosis, and for the inflammatory recruitment and fibrosis in NASH patients with or without obesity and insulin resistance [61–63], as well as in a wide variety of animal models [64–67]. Taken together, unhealthy dietary habits may promote steatohepatitis directly by modulating hepatic triglyceride accumulation and antioxidant activity, and indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism.

Another reported risk factor is cigarette smoke, which contains more than 4000 toxic chemicals, including tar, nicotine, and carbon monoxide [68–70]. An association of cigarette smoking with MetS, such as IR, diabetes, and dyslipidemia, has been reported [71–73]. As we know, MetS is a major risk factor for the development of NAFLD, and the question of whether cigarette smoking impacts the development of NAFLD has been raised. Azzalini *et al.* [74] reported that cigarette smoking caused significant oxidative stress and hepatocellular apoptosis, and worsened the severity of NAFLD, in obese Zucker rats. Their results indeed provided important data for improving our understanding of the relationship between cigarette smoking and NAFLD. However, whether this association holds true in humans remains unclear; moreover, it is not clear whether cigarette smoking independently increases the risk for NAFLD. In a large-scale retrospective study, Hamabe *et al.* [75] found that cigarette smoking was a risk factor for NAFLD development independent of MetS risk factors.

In addition, lack of exercise is a major cause of chronic diseases, including NAFLD [76]. Therefore, when unhealthy dietary patterns and habits are coupled with a sedentary Western lifestyle, caloric imbalance can occur, resulting in increased weight gain in most individuals. The increasing prevalence of overweight/obesity is associated with the epidemic of NAFLD.

9.4 PATHOGENESIS OF NAFLD AND NASH

The pathogenesis of NAFLD and its progression to NASH has not been fully described. An older concept of NASH pathogenesis, the so-called "two-hit" hypothesis of Day and James [77], proposed that hepatocyte triglyceride accumulation resulting from MetS (obesity, IR, and diabetes) is what leads to steatosis (the "first hit"), and that the lipid-laden liver is then vulnerable to injurious processes ("second hit" insults) such as cytokines and oxidative stress. Damaged and dying hepatocytes and/or recruited and activated inflammatory cells, such as Kupffer cells, generate other signals (cytokines, growth factors, and oxidative stress) which activate hepatic stellate cells, with resultant development of liver fibrosis and cirrhosis [78,79].

9.4.1 Mechanism of Steatosis

Steatosis is the excessive accumulation of triglycerides (>5% of liver weight) in the liver [80]. Accumulation of fat in the liver represents an imbalance in hepatic lipid turnover. The liver plays a pivotal role in lipid metabolism. It absorbs circulating free fatty acids and other lipids that arise from intestinal uptake/dietary sources, from lipolysis of peripheral storage sites (adipose tissue), and from *de novo* synthesis (lipogenesis). The liver then exports the lipids for storage in adipose stores as triglyceride-rich very low-density lipoproteins (VLDLs) [81]. Steatosis occurs when fatty acid supplies to the liver (from dietary intake, peripheral lipolysis, and *de novo* lipogenesis) exceed hepatic fatty acid elimination (via oxidation, re-esterification, and excretion as VLDLs) [80,81].

Kinetic studies have indicated that approximately 75% of hepatic lipids in obese patients with NAFLD come from peripheral sites (60% from non-esterified free fatty acids by lipolysis and 15% from diet), with approximately 25% arising from *de novo* lipogenesis [82]. The process of *de novo* lipogenesis is governed by several nuclear transcription factors activated by insulin (in the case of sterol regulatory element binding proteins [SREBPs], 1 and 2) and glucose (in the case of carbohydrate-responsive sterol regulatory element binding protein [ChREBP], 1) [80,83]. Both SREBP1 and ChREBP activate fatty acid synthase, the rate-limiting step in the biosynthesis of long-chain fatty acids which are ultimately esterified to form triglycerides, while SREBP2 regulates cholesterol biosynthesis. These pathways provide a partial explanation of why IR and premetabolic syndrome (which is

hyperinsulinemia and glucose intolerance) are strongly associated with steatosis. Several studies have suggested that there is increased hepatic lipogenesis in hepatic steatosis [84]. Increased lipogenesis may have a dual effect: increased triglyceride synthesis and decreased fatty acid oxidation through production of malonyl-CoA [84], both leading to increased triglyceride content in fatty liver. Sanyal *et al.* reported that β-oxidation of fatty acids in the liver was increased in patients with NASH [85]. However, this increase might not sufficiently overcome the elevated rates of hepatic fatty acid synthesis.

Triglyceride accumulation in hepatocytes was considered to be the major pathogenic trigger in the development of NAFLD. Diacylglycerol acyltransferase 2 (DGAT2) catalyzes the final step in hepatocyte triglyceride biosynthesis. Suppression of DGAT2 reverses diet-induced hepatic steatosis and IR [86], and attenuates hyperlipidemia [87]. However, recent findings suggest that triglyceride synthesis may not be harmful to hepatocytes. Rather, it provides a useful mechanism for buffering free fatty acid accumulation [88]. Yamaguchi *et al.* [88] showed that inhibiting triglyceride synthesis by suppressing DGAT2 did improve hepatic steatosis, yet it exacerbated liver damage and fibrosis in obese mice with non-alcoholic steatohepatitis. Lipotoxicity arises when hepatic triglyceride synthesis is unable to accommodate increased free fatty acid accumulation.

Additionally, IR raises serum insulin and increases serum-free fatty acid levels. In the presence of a steatotic liver, the hyperinsulinemic state fails to suppress adipose-free fatty acid flux, resulting in these free fatty acids being taken up by the liver, driving triglyceride production, and ultimately perpetuating more hepatic steatosis and inflammation when the mechanisms for lipid storage in adipocytes become overwhelmed [89]. Several studies have clearly indicated that the development of NAFLD and MetS is more closely linked to the pattern of fat distribution than to total body fat. In particular, central (or visceral) adiposity is strongly implicated in the development of both hepatic steatosis and MetS [78,90]. Taken together, the following four mechanisms are possible causes of lipid accumulation within the liver: (1) increased delivery and uptake into hepatocytes of long-chain fatty acids due to excess dietary intake or release from adipose tissue; (2) increased *de novo* hepatic fatty acid and triglyceride synthesis; (3) failure of VLDL synthesis and triglyceride export; and (4) failure of fatty acid elimination due to impaired hepatic β-oxidation.

9.4.2 What Promotes Steatosis to Steatohepatitis?

In the setting of stressed and hypertrophic adipocytes caused by overnutrition and obesity, increased visceral adipose tissue was found to induce the recruitment of inflammatory cells, particularly macrophages, resulting in dysregulation of adipocytokines (TNF-α, leptin, resistin, and, most notably, adiponectin) [91]. Visceral adipose tissue secretes more pro-inflammatory cytokines (TNF-α, IL-6, and MCP1), and this, coupled with direct drainage to the liver via the portal circulation, emphasizes the ability of visceral adipose tissue to directly impair hepatic insulin signaling and promote inflammation [81,91]. TNF-α can activate both nuclear factor-kappa B (NF-κB) and c-jun *N*-terminal kinase, promoting serine phosphorylation of an insulin receptor substrate which directly impairs insulin signaling. Additionally, MCP1 can activate inflammatory pathways and promote hepatocyte triglyceride accumulation directly. The NF-κB signaling pathway, in particular, plays a role in the pathogenesis of a wide variety of liver conditions, such as steatohepatitis [92]. NF-κB, commonly referred to as the p65/p50 protein heterodimer, accumulates in the initiation phase of inflammation. It has been reported that the NF-κB activation pathway is involved in the pathogenesis of inflammation in the non-obese and non-diabetic NASH model [80].

Significant hepatocyte death (apoptosis or necrosis) is a feature of NASH [93,94], which triggers regenerative mechanisms to replace dead hepatocytes. However, aberrant repair in some individuals eventually leads to activation of hepatic stellate cells and their transformation to myofibroblasts, and to hepatic recruitment of immune cells that produce pro-inflammatory and profibrogenic cytokines [79].

9.5 ANIMAL MODELS

Studies of NAFLD/NASH using human materials have limitations, because the occurrence and progression of NAFLD/NASH requires a period of several decades, and ethical limitations exist regarding administering drugs to patients or collecting their liver tissue. Animal models of NAFLD/NASH give crucial information, not only for elucidating the pathogenesis of NAFLD/NASH but also for examining therapeutic effects of various agents [95]. An ideal animal model of NAFLD/NASH should reflect the hepatic histopathology and pathophysiology of human NAFLD/NASH. Accordingly, the liver of the NASH animal model should show steatosis, intralobular inflammation, hepatocellular ballooning, perisinusoidal fibrosis in zone 3, and susceptibility to liver tumors. Furthermore, the animal should show metabolic abnormalities such as obesity, IR, fasting hyperglycemia, dyslipidemia, and an altered adipokine profile [95]. Established animal models of NAFLD/NASH are classified into genetic models, nutritional models, and models with a combination of genetic and nutritional factors. Here, we introduce several representative and popular animal models.

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