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TOPIC HIGHLIGHT

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Dietary habits and behaviors associated with nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the most frequent causes of health problems in Western (industrialized) countries. Moreover, the incidence of infantile NAFLD is increasing, with some of these patients progressing to nonalcoholic steatohepatitis. These trends depend on dietary habits and life-style. In particular, overeating and its associated obesity affect the development of NAFLD. Nutritional problems in patients with NAFLD include excess intake of energy, carbohydrates, and lipids, and shortages of polyunsaturated fatty acids, vitamins, and minerals. Although nutritional therapeutic approaches are required for prophylaxis and treatment of NAFLD, continuous nutrition therapy is difficult for many patients because of their dietary habits and lifestyle, and because the motivation for treatment differs among patients. Thus, it is necessary to assess the nutritional background and to identify nutritional problems in each patient with NAFLD. When assessing dietary habits, it is important to individually evaluate those that are consumed excessively or insufficiently, as well as inappropriate eating behaviors. Successful nutrition therapy requires patient education, based on assessments of individual nutrients, and continuing the treatment. In this article, we update knowledge about NAFLD, review the important aspects of nutritional assessment targeting treatment success, and present some concrete nutritional care plans which can be applied generally.

Key words: Nonalcoholic fatty liver disease; Nutritional therapy; Carbohydrates; Fatty acids; Cholesterol

Core tip: The onset and development of nonalcoholic fatty liver disease (NAFLD) are closely associated with dietary habits and lifestyle; therefore, nutritional therapeutic approaches are required for these patients and those at risk of developing NAFLD. This article reviewed current nutritional status of NAFLD patients and the important aspects of nutritional assessment targeting treatment success.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a major health problem in Western countries, affecting 30% of the adult population and 60%-80% of patients with diabetes mellitus and/or obesity[1,2]. The 2011 National Health and Nutrition Examination Survey reported that the rates of NAFLD, obesity, and type 2 diabetes have increased coordinately over time since the 1988-1994 survey[2], indicating that NAFLD is associated with obesity and type 2 diabetes.

In addition, the prevalence of NAFLD in children and adolescents is increasing, and has been reported to be about 10%[3-5]. Although genetic factors have been associated with the onset of pediatric NAFLD[6], the most important risk factor in children, as in adults, is overweight, with the prevalence of NAFLD higher in obese than in non-obese children[3,7-9]. Moreover, nonalcoholic steatohepatitis (NASH) has been diagnosed in 3% of children and adolescents[5].

About 20%-25% of adults with NASH have been reported to develop liver cirrhosis within 10 years[1], with hepatocellular carcinoma occurring in 8.6% of cirrhotic NASH patients within 12 years[10] or in 11.3% within 5 years[11]. A recent meta-analysis showed that, compared with patients with simple steatosis, those with NASH have higher liver-related mortality rates, with an OR for patients with NASH of 5.71 and an OR for patients with NASH and advanced fibrosis of 10.06[12]. In addition, NAFLD is considered as a risk factor for cardiovascular disease (CVD), because many patients with NAFLD develop metabolic disorders[13]. A longitudinal study of 129 patients with biopsy-proven NAFLD who were followed for a mean of 13.7 years found that mortality from cardiovascular events was higher than liver-related mortality, with the overall mortality of patients with NASH being twice that of a matched reference population[14]. Similarly, a cohort study of Swedish patients with NAFLD who were followed-up for a mean of 28 years showed that mortality risks were higher for patients with NAFLD (OR = 1.69) and NASH (OR = 1.86), compared with the general Swedish population, and that CVD is the most frequent cause of death[15]. Another prospective, nested, case-control study in 2103 patients with type 2 diabetes without diagnosed CVD at baseline who were followed-up for a mean 5 years found that the presence of NAFLD was significantly associated with an increased CVD risk (OR = 1.84) and that this relationship was independent of classical risk factors[16].

Because NAFLD develops as early as childhood and was found to exacerbate other conditions and worsen patient prognosis, treatment methods are urgently needed. Nutrition therapy is the basic form of treatment for patients with NAFLD and those at risk of developing this disorder. Therefore, all clinical staff involved in NAFLD prevention or treatment should understand nutritional strategies for dealing with NAFLD.

BEHAVIORAL SCIENCE AND MULTIDISCIPLINARY NUTRITIONAL CARE FOR SUCCESSFUL NUTRITION THERAPY

NAFLD is closely associated with obesity. Put simply, obesity results from greater energy intake than consumption, with excessive energy accumulated as fat. NAFLD patients with excess energy intake have shown improvements following weight loss resulting from restricted energy intake; *e.g.*, 600-800 kcal/d, 25-30 kcal/kg (standard weight) per day, or baseline minus 500-1000 kcal/d (Table 1)[17-24]. Although restricted diets are clinically effective in the short-term, long-term energy and weight control is very difficult for many patients[25]. For example, a 6-mo nutritional intervention was successful in only 54.8% of patients with NAFLD[24], perhaps because patients differ in grade of motivation and preparation for the therapy.

Generally, a desirable health behavior is attained by changes that progress through five stages evaluated by the transtheoretical model: (1) a precontemplation stage, in which a patient has no intention of changing in the foreseeable future; (2) a contemplation stage, in which a patient intends to change, but not soon; (3) a preparation stage, in which a patient intends to change during the next month; (4) an action stage, in which a patient changes; and (5) a maintenance stage, in which a patient has maintains the change for at least 6 mo[26,27]. The transtheoretical model, a popular concept in the area of health psychology, has been applied in patients with smoking, obesity, human immunodeficiency virus infection, and so on. The answers to the different questions are summed up to evaluate motivation to change according to the transtheoretical model of upper five stages of change, using 10 statements; two for each stage. The different stages of change have been theorized to predict treatment participation to programs and dropout, as well as efficacy and long-term maintenance of improvement. An evaluation of the intake of low-fat health food diets by obese patients with diabetes using these five stages found that 48.2% of male patients and 25.0% of female patients were at the precontemplation and contemplation stages[28,29]. This trend was similar in patients with NAFLD. Dietary habits and physical activity in NAFLD patients were reported to be associated with the stages of change evaluated by the transtheoretical model, in which highest 36.0% of patients were at the contemplation stages[30]. Therefore, although all NAFLD patients require nutrition therapy, more than 50% will not readily accept the need for or practice nutrition therapy. Thus, prior to initiating nutrition therapy, it is important to assess whether an individual patient is at a receptive stage for it. Behavioral counselors should therefore work flexibly with patients. For example, motivation by raising a patient's consciousness level is important during the precontemplation stage. During the contemplation stage, it is necessary for the

Table 1 Effect of nutritional intervention on nonalcoholic fatty liver disease

Study design	No. of cases	Duration (mo)	Improved items	Ref.
Balanced hypocaloric diet, exercise	9	9-30	ALT, fatty change	[19]
Very-low calorie diet	41	4-23	fatty change	[20]
Weight reduction (retrospective)	39	-	ALT	[21]
Diet (25 cal/kg•ibw), exercise	25	3	AST, ALT, ChE, TC, FPG fatty change	[22]
Diet (add 300 mg/d)	22	12	ALT, TGF-β, fatty change inflammation, fibrosis	[23]
Diet (baseline minus 500-1000 cal/d)	31	6	ALT, GGT, HDL-C, HOMA-IR WHR, fatty change, visceral fat	[24]

Ibw: Ideal body weight; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ChE: Choline esterase; TC: Total cholesterol; FPG: Fasting plasma glucose; TGF: Transforming growth factor; GGT: γ-glutamyl transpeptidase; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance; WHR: Waist-to-hip ratio.

patient to evaluate the effects of behavior modification, strengthening each patient's motivation and supporting his/her decision making. A recent randomized controlled trial in patients with NASH found that 48-wk-long lifestyle intervention, using a combination of diet, exercise, and behavior modification, significantly improved patient histologic activity score, body weight, body mass index (BMI), and serum alanine aminotransferase (ALT) levels[31]. Patients discussed dietary and health problems during weekly group sessions, and their nutritional education employed several techniques of behavioral science, including self-monitoring of food eaten, body weight, and exercise; stimulus control techniques; and education to prevent relapse[31-33].

Similarly, in patients with pediatric NAFLD, a 6-mo-long lifestyle intervention, consisting of physical exercise, dietary counseling, and behavioral counseling, improved steatosis and serum ALT levels[34]. In another study on obese pediatric NAFLD patients, lifestyle intervention, consisting of physical activity, nutritional education, and behavioral therapy, for 1 year decreased BMI and serum ALT levels, with improvements maintained 1 year after the completion of this intervention[35]. Reductions in BMI and ALT not only improved the grade of NAFLD in these patients but prevented its progression to steatohepatitis[36]. These findings indicate that nutritional education employing behavioral methods conducted by a multidisciplinary nutritional care team is extremely useful and effective.

ASSESSMENT OF THE MAIN CAUSE OF EXCESS ENERGY INTAKE

For nutritional therapy to yield better outcomes, more detailed assessments of excess energy intake are needed. Some eating patterns are closely associated with excessive intake, such as increased dietary volume, high energy-dense diets, inappropriate mealtimes and manner of eating, and excessive intake of specific nutrients. It is important to determine the factor(s) crucial for each patient and to supply each patient with individual knowledge for appropriate dietary interventions.

Increased dietary volume

Increased dietary volume may be due to, for example, a high frequency of eating outside the home, larger food portions, and the diffusion of all-you-can-eat style. Energy intake during a meal is usually larger while eating out than while eating at home. Eating out was reported to increase overall energy intake by 14% in 1977-1978, a rate that increased to 32% during 1994-1996[37]. In addition, portion sizes of salty snacks, hamburger, soft drinks, fried potatoes, and Mexican food eaten outside the home in 1977-1978, 1989-1991, and 1994-1998 increased over time in almost all examined subjects[38]. Enlarged meal volume increases energy intake, resulting in obesity and NAFLD[39]. Energy intake also tends to be higher at all-you-can-eat restaurants because various kinds of foods are displayed. Actually, an increase in the variety of dishes at a meal has been found to enhance food intake by at least 25%, because of the variety of sensory properties of the foods, such as taste, palatability, and flavor[40-43]. Food intake may be reduced by reducing the frequency of eating out and of eating at all-you-can-eat establishments. Moreover, when eating at home, the food/energy requirement in a meal should be habitually arranged beforehand, by, for example, the distribution of individual portions.

High energy-dense diets

Fast-foods, meals eaten out, and fried foods are representative of a high energy-dense diet. A study assessing the influence of fast-foods on liver function found that young adults with a daily energy intake of 2273 ± 558 kcal (fat: 36% ± 5.7%, sugar: 95 ± 42 g) given fast-food-based hyperalimentation of 5753 ± 1495 kcal (fat: 43% ± 6.8%, sugar: 285 ± 117 g) for 4 wk showed an increase in body weight from 67.6 ± 9.1 to 74.0 ± 11.0 kg and an increase in serum ALT levels from 22.1 ± 11.4 to 97 ± 103 U/L[44]. These findings indicated that a high energy-dense diet can increase energy intake easily and markedly, resulting in obesity and NAFLD. In the CARDIO study, the habitual eating of fast-foods was assessed in young adults at baseline and 15 years later, and the association of a fast-food diet with weight gain and insulin resistance was analyzed[45]. A higher frequency of fast-foods at baseline and at the end of the 15-year follow-up resulted in greater weight gain, independent of race or ethnicity, with the frequency of eating fast-foods positively correlated with mean energy intake[45,46].

Official rules for the fast-food industry, such as energy restriction, increasing quantities of vegetables, and non-inclusion in children's meals of toy lagniappes, have been introduced in several countries. Thus, prior to starting a patients with NAFLD on nutrition therapy, the frequency of eating fast-foods, fried foods, and eating out should be assessed beforehand. Decreasing all of these may prevent the development and/or progression of NAFLD. It is recommended that these individuals eat at home more frequently and that they consume a low energy-dense diet, with higher quantities of vegetables.

Inappropriate mealtimes and eating manners

Inappropriate patterns of food intake, including the habit of eating too much at evening meals, eating at night, missing breakfast, and eating too rapidly, are often seen in patients with obesity and NAFLD. The night-eating syndrome is frequently observed in obese patients[47]. Night workers and shift workers were recently shown to be at high risks of obesity, metabolic syndrome, and fatty liver disease[48-50]. Food intake at unusual times by shift workers induces chronic sleep disorder and increased desire for fats, resulting in obesity and diabetes[51]. This phenomenon may be due to the activity of the clock genes. Male Period gene-mutant mice gain significantly more body mass than wild-type controls on high-fat diet[52].

Missing breakfast, especially by children and adolescents, has been associated with obesity[53]. Missing breakfast usually increases food intake at other mealtimes. Mice with a greater energy intake in the evening meal had a higher body weight, more visceral fat, and higher fasting blood glucose levels, whereas all of these were lowest when the breakfast:evening meal energy ratio was 3:1[54]. Whenever possible, therefore, patients on nutrition therapy for NAFLD should be started on a diet in which energy intake in the evening and night-time is restricted and intake at breakfast should be enhanced. However, the problem of shift work cannot be resolved easily.

Individuals who eat more quickly eat more food and have a lessened feeling of satiety than those who eat more slowly (20-30 chews per mouthful)[55]. Persons who eat faster have a higher mean BMI and an increased rate of BMI[56,57]. Increased mastication of each mouthful has been reported to prevent overeating and promote general and oral health[58]. Similarly, more than 20 chews per mouthful should be recommended during nutritional education for NAFLD patients to prevent overeating.

OVER-INGESTION OF CARBOHYDRATES

Carbohydrates are classified as simple and complex, with over-ingestion of simple carbohydrates, such as sucrose and fructose, being a major cause of NAFLD. Consumption of soft drinks, including those containing sucrose, is significantly increasing worldwide[59]. In comparison between NAFLD and non-NAFLD cases, mean daily consumption and mean frequency of soft drinks is at least two fold higher in patients with than without NAFLD[60-62]. The degree of ultrasonography-evaluated hepatic fatty changes was found to correlate with the increase in the number of consumed bottles of soft drinks, indicating that soft drink consumption is strongly predictive of fatty liver[62]. Moreover, the rates of consumption of simple and total carbohydrates were found to be higher in patients with NASH than in those with simple steatosis[17]. Excess intake of simple carbohydrates was found to rapidly induce elevated serum glucose levels and reactive hypoglycemia, resulting in a sensation of hunger, increasing appetite, and finally resulting in hyperphagia[63]. Excess intake of simple carbohydrates is closely associated with obesity and steatosis, perhaps through the activation of sterol regulatory element-binding protein-1c (SREBP-1c), a transcription factor that enhances the expression of enzymes associating with fatty acid synthesis[64].

The basic strategy in nutritional care is to understand each patient's habits of consuming foods and soft drinks, including simple carbohydrates, and to restrict the intake of these foods and drinks, if excessive amounts have been ingested[65]. Restricting the intake of soft drinks requires patient motivation, although governments can also act by restricting these items. Taxation of soft drinks in the United States has been proposed to decrease their consumption and to provide revenue for national health programs[59,66,67].

In contrast, appropriate intake of complex carbohydrates, especially that of whole grains, may prevent the development and/or progression of NAFLD, because these grains contain antioxidative vitamins, minerals, and dietary fibers, in addition to carbohydrates[68]. Indeed, intake of whole grains may decrease visceral fat and improve obesity, dyslipidemia, and metabolic syndrome[69,70]. Moreover, a meta-analysis showed that whole grains reduced the risks of heart disease and type 2 diabetes; serum levels of fasting insulin, fasting glucose, and lipids; and body weight, all of which are associated with the pathogenesis of NAFLD[71-75]. Thus, paradoxically, a nutritional care plan for patients with NAFLD should seek to restrict carbohydrates, while increasing ingestion of whole grains.

OVER-INGESTION OF LIPIDS

Lipid over-ingestion results in excess energy intake and body fat accumulation. Increased visceral fat increase the inflow of free fatty acids into the liver, resulting in hepatic steatosis[76]. Over-ingestion of saturated fatty acids is thought to induce insulin resistance and type 2 diabetes[77-80]. A 7-d nutritional survey of diet showed that ingestion of saturated fatty acids was significantly greater in NAFLD patients than in healthy controls[81]. Moreover, intake of saturated fatty acids, as well as of lipids, was reported significantly greater in NAFLD and NASH patients than in healthy individuals[17]. When patients with NAFLD were randomly allocated an isoen-

ergetic low-fat/low-saturated fat/low-glycemic index (GI) diet (LSAT: 23% fat/7% saturated fat/GI < 55) or a high-fat/high-saturated fat/high-GI diet (HSAT: 43% fat/24% saturated fat/GI > 70), with liver fat quantitated by magnetic resonance spectroscopy before and after 4 wk on the LSAT and HSAT diets, those in the LSAT, but not those in the HSAT group showed significant reductions in liver fat[82]. In other animal studies, a high-fat diet induced hepatic steatosis and inflammation, insulin resistance, and tumor necrosis factor α (TNFα) elevation[83-85]. These changes may be associated with the activation of peroxisome proliferators-activated receptor γ (PPARγ)[64].

Thus, over-ingestion of lipids, especially saturated fatty acids, is one of the most important risk factors for NAFLD onset and development. Therefore, before addressing NAFLD, it is recommended that patients' eating habits be assessed, including patient intake of dairy products; fats in meat, butter and margarine; chocolate, and snack foods. If any of these foods are consumed excessively, its quantity should be reduced. Clinically, more concrete nutritional care plans are necessary; *e.g.*, bacon and sirloin, which contain considerable quantities of fat, should be switched to leg meat, fillet, or, if appropriate, to fish containing polyunsaturated fatty acids (PUFAs); and butter and margarine should be switched to the calorie-half products.

OVER-INGESTION OF CHOLESTEROL

Over-ingestion of cholesterol has been regarded as a critical cause of NAFLD[86-89]. For example, a 7-d nutritional survey found that dietary cholesterol intake was significantly greater in NASH patients than in healthy subjects[81]. In addition, our investigation of the dietary records of obese and non-obese NAFLD patients found that cholesterol ingestion was significantly greater in NAFLD patients than in healthy controls[90]. Interestingly, non-obese NAFLD patients ingested more cholesterol than obese NAFLD patients[90], indicating that cholesterol intake is dietetically essential for NAFLD onset/progression independent of obesity. These findings are supported by animal experiments, in which a high-cholesterol diet within the normal energy range induced the onset of non-obese NAFLD in mice[91-93]. Although the mechanisms have not been determined, the hepatic metabolic products of cholesterol, oxysterols, are ligands of liver X receptor α, which activates SREBP-1c and the *de novo* synthesis of fatty acids[94,95]. Although several studies reported no significant differences in cholesterol intake levels between NAFLD patients and healthy subjects, those studies did not assess dietary records but used food frequency questionnaires[96,97]. Future studies are needed to assess cholesterol intake levels and the clinical effects of cholesterol restriction in larger populations of patients with NAFLD. Over-ingestion of dietary cholesterol should be suspected in non-obese patients with NAFLD, and their dietary intake of food high in cholesterol, such as eggs, fish eggs, liver, and cakes, should be assessed. Reduction of cholesterol intake has also been recommended to prevent the development of CVD, regardless of the presence of obesity[98,99].

DEFICIENCY OF POLYUNSATURATED FATTY ACIDS

PUFA intake is lower in patients with NAFLD than in healthy individuals, regardless of excessive lipid intake[17,81]. Moreover, we found that PUFA intake was significantly lower in non-obese than in obese NAFLD patients[90]. These findings suggest that dietary contents are unbalanced in patients with NAFLD and that PUFA deficiency is involved in the onset and progression of NAFLD. PUFAs can improve insulin sensitivity by decreasing hepatic TNFα, can repress fatty acid synthesis by negatively controlling SREBP-1c, and can enhance fatty acid oxidation by positively controlling PPARα[100,101]. In some studies in animal models, administration of n-3 PUFAs reduced liver fat and improved hepatic inflammation[102,103]. These results are supported by nutritional interventions in patients with NAFLD. Although saturated fatty acids increase the likelihood of NAFLD development, PUFAs may be beneficial for these patients. For example, treatment of NAFLD patients for 12 mo with 1 g/d of n-3 PUFAs decreased ultrasonography-detected liver fat[104]. Moreover, in a study of patients receiving diet therapy with or without 2 g/d n-3 PUFAs for 6 mo, those administrated n-3 PUFA showed greater decreases in liver fat[105,106]. Furthermore, an 8-wk-long, double blind, crossover trial of 4 g/d n-3 PUFA and placebo showed that the accumulated liver fat decreased significantly in the n-3 PUFA group[107]. In none of these studies did n-3 PUFA show any adverse effects. Moreover, n-3 PUFAs improved risk factors for CVD, including markers of insulin resistance and inflammation, as well as serum levels of ALT, lipids and glucose. Deliberate supplementation with PUFA, especially n-3 PUFA, may be an effective form of nutrition therapy in patients with NAFLD, and may also prevent CVD[108,109]. However, combination with appropriate energy intake is a prerequisite, with the basic nutritional approach consisting of increasing the frequency of eating n-3 PUFA-rich fish in place of meat containing high quantities of saturated fatty acids.

DEFICIENCY OF VITAMIN E

Progression from NAFLD to NASH is commonly explained by the two-hit theory[110], with oxidative stress considered as a second hit factor[111-113]. Intake of vitamin E has been reported deficient in NAFLD and NASH patients compared with healthy subjects[81,114]. Moreover, in children, vitamin E intake was negatively correlated with the grade of liver fat. Total peroxide level and oxidative stress index were found to be positively correlated, and total antioxidant status negatively correlated,

with fibrosis scores in patients with NAFLD[115]. These results are supported by other studies, which found that serum markers of oxidative stress were independent prognostic indicators of hepatic fibrosis[116-118]. Patients with NAFLD and NASH require more vitamin E to counteract increases in oxidative stress. Even if NAFLD patients take amounts of vitamin E equivalent to those taken by healthy individuals, patients may experience a net shortage, with reduced serum levels. However, many foods with high vitamin E contents, including some oils and fats, liver, and fish eggs, also contain large amounts of cholesterol, and greater quantities of these foods are ingested by NAFLD patients than by healthy individuals[18]. Although vegetables, especially green and yellow vegetables, do not have high vitamin E contents, they are important sources of this nutrient. Because vegetable intake by NAFLD patients is generally reduced[18], NAFLD patients with vitamin E deficiency should ingest higher quantities of green and yellow vegetables.

Patients who have dietary compliance problems should be administered vitamin E supplements. High-dose vitamin E supplementation has been reported to lower serum ALT levels in patients with NAFLD[23], and a randomized control study of vitamin E supplementation for 2 years to NASH patients without diabetes found that histologic activity score improved in a significantly higher percentage of the vitamin E than of the placebo group (43% *vs* 19%, $P = 0.001$)[119], demonstrating that vitamin E has clinical antioxidative effects. However, administration of high amounts of vitamin E may induce cerebral vascular disease and increase all-cause mortality[120,121]. A recent meta-analysis found that vitamin E treatment for 2 years of patients with NAFLD improved histology score, but led to a deterioration in insulin resistance and an increase in serum triglyceride levels[12]. In the United States practice guideline for the diagonosis and management of NAFLD, (1) Vitamin E (α-tocopherol) administered at daily dose of 800 IU/d improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population, and (2) Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis. Thus, while vitamin E is an important nutrient that can improve disease activity in patients with NASH, it also has the potential to cause other clinical problems. Patients receiving high-dose vitamin E supplementation should be closely monitored. According to recent studies, supplementation of 300 mg/d vitamin E seems to be safe and effective even in patients with fibrosis and/or impaired fasting glucose[23,122,123].

DEFICIENCY OF VITAMIN D

Vitamin D plays an important part in the processes of inflammation and autoimmunity. Deficiencies in vitamin D can result in insulin resistance, metabolic syndrome, and NAFLD[124]. Many obese children ingest a high-energy diet with low vitamin and mineral content, and are not sufficiently exposed to sunlight[125]. For example, serum vitamin D levels were low in 55% of young Americans[126]. Rats fed a Westernized diet (WD: high-fat/high-fructose corn syrup) with vitamin D depletion (29% compared with controls) had significantly poorer liver fat, lobular inflammation, and NAFLD activity scores than rats fed a WD, a low-fat diet (LFD), or a LFD with vitamin D depletion[127]. In humans, deficiency of vitamin D has been correlated with the severity of NAFLD activity score and hepatic fibrosis[128], perhaps owing to the greater oxidative stress resulting from vitamin D deficiency[129]. Hepatic expression of vitamin D receptors, CYP2R1 and CYP 27A1, has been negatively correlated with the severity of steatosis, inflammation, and NAFLD score in patients with NAFLD[130].

Taken together, these findings indicate that excess energy intake accompanied by vitamin D deficiency enhances the onset and progression of NAFLD/NASH. Thus, the status of vitamin D intake and serum vitamin D levels should be ascertained prior to beginning nutritional therapy for NAFLD. Patients with vitamin D deficiency should ingest foods with a high vitamin D content, such as fishes and mushrooms, at least once per day.

NUTRITIONAL THERAPY WITH PROBIOTICS

Probiotics are live bacteria or foods containing them that may confer a health benefit on the host by regulating intestinal microbial flora. Intestinal microbial flora change with BMI and eating habits[131,132]. Alteration of the enteral environment by probiotics has been shown to improve the pathology of NAFLD[133,134]. In animal models, administration of probiotics had desirable clinical effects, including decreases in liver fat and serum ALT and lipid levels, and improvements in inflammation, liver fibrosis, oxidative stress, and insulin resistance[132-142]. Serum levels of ALT, malondialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE), and TNFα have been reported to be decreased in NAFLD patients administered probiotics (Lactobacillus acidophilus, bifidus, rhamnosus, plantarum, salivarius, bulgaricus, lactis, casei, breve mixed with prebiotic fructooligosaccharide and vitamins as B_2, B_{12}, B_6, D_3, C, and folate) for 2 mo[143]. In addition, the probiotic VSL#3 had beneficial effects on lipid peroxidation markers (MDA, 4-HNE) in NAFLD patients[144]. A randomized, double-blind, placebo-controlled clinical trial found that administration of probiotics (Lactobacillus bulgaricus and Streptococcus thermophiles) for 3 mo significantly decreased serum aspartate aminotransferase, ALT, and γ-glutamyl transpeptidase levels in patients with NAFLD[145], in good agreement with results in animal models. Probiotic treatment can be included in nutrition therapy for NAFLD. Future studies investigating

the effects of probiotics on other outcomes in patients with NAFLD, such as inhibition of hepatic fat accumulation and inflammation, as well as studies investigating foods containing probiotics, such as yogurt and lactic acid drinks, are expected.

CONCLUSION

Because the onset and development of NAFLD are closely associated with dietary habits and lifestyle, nutritional therapeutic approaches are required for these patients and those at risk of developing NAFLD. This article reviewed current nutritional strategies and their effects and problems.

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