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Nutritional Recommendations for Patients with Non-Alcoholic Fatty Liver Disease: An Evidence Based Review



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Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver disorders due to abnormal fat deposition in the liver. These range histopathologically from simple steatosis to steatohepatitis (NASH) which can progress to cirrhosis and end stage liver disease. NAFLD is the most common cause of chronic liver disease in the developed world and is generally a component of the underlying “metabolic syndrome.” It is likely to emerge as the most common cause of liver disease associated mortality in the next decade. Currently, there is no specific drug therapy approved for the treatment of this condition. This article reviews the role of weight loss measures and nutritional supplements such as antioxidants and n-3 polyunsaturated fatty acids in the treatment of NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the developed world (1). NAFLD refers to a spec-

trum of liver disorders occurring due to abnormal fat deposition in the liver, which ranges in severity from simple hepatic steatosis with no inflammation, to steatohepatitis (NASH) which can progress to liver cirrhosis. The diagnosis of NAFLD by definition implies the exclusion of significant alcohol intake (i.e., >140 gm/week in men; >70 gm/week in women). Histologically, it is characterized by a spectrum of findings ranging from macrovesicular steatosis alone, mixed portal and lobular inflammation of varying degrees, balloon-

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ing degeneration of hepatocytes with perisinusoidal deposition of collagen, and finally full blown cirrhosis (2,5). Recent epidemiologic studies support the role of antecedent NASH in causing about two-thirds to three-fourths of all cryptogenic cirrhosis cases (3).

NAFLD is generally found as a component of the “metabolic syndrome” which is characterized by central obesity, hypertension, hyperlipidemia, and impaired glucose tolerance. Up to 90% of patients with NAFLD have at least one of these features (4). The incidence of NAFLD and NASH in the general population varies widely depending on the test used to diagnose it. Liver biopsy remains the gold standard of diagnosis. However, different tests, including liver enzymes (AST, ALT) and imaging (liver ultrasound, MR spectroscopy), have been used. Studies looking at the Third National Health and Nutrition Examination Survey (NHANES III) using AST and ALT as criteria for NAFLD (after excluding alcohol and hepatitis B, C as causes) found a prevalence of 5.4% in the U.S population (6,7). However, liver enzymes have been shown to be non-specific and poorly sensitive for chronic liver disease (8). Use of liver ultrasound to diagnose hepatic steatosis has shown a prevalence of NAFLD ranging from 57–75% in obese, non-drinking patients (9). Use of MR spectroscopy in a large multi-ethnic patient population shows a prevalence of NAFLD of 34% in the general population with major ethnic and gender differences (10).

NATURAL HISTORY OF NAFLD

One of the best studies to date looking at the natural history of NAFLD in the general population was done in the Mayo Clinic by Adams et al. A total of 420 patients in Olmstead County, Rochester, diagnosed with NAFLD, using imaging or with a liver biopsy, were followed for a median period of 7 years. Twenty-one patients (5%) developed cirrhosis during this period, and thirteen (3.1%) developed complications of cirrhosis, including two patients who developed hepatocellular cancer (11). Even though only a minority (<10%) of patients with NAFLD develop cirrhosis and end stage liver disease, the sheer numbers of patients who have NAFLD in the general population make this a significant health care concern.

PATHOGENESIS OF NAFLD

Excess energy intake and obesity, in combination with different genetic and environmental factors, can lead to the development of insulin resistance. A combination of insulin resistance, along with excess accumulation of free fatty acids (FFA) and increased intracellular formation of toxic lipid metabolites (such as products of lipid peroxidation), is thought to elicit an inflammatory response that triggers the progression to NASH. The accumulation of triglycerides themselves in the hepatocytes is merely a marker for the deranged lipid metabolism and indicates increased lipid trafficking (12). Since lipotoxicity is thought to be a major player in the pathogenesis, both dietary modifications and exercise seem theoretically the best options for preventing the progression to NASH and for management of NASH once it develops. This review focuses on the nutritional interventions that can potentially make a difference in the management of this disease.

DIETARY MODIFICATIONS AND LIFESTYLE CHANGES IN NAFLD

Several studies have shown beneficial effects of dietary modification, weight loss and exercise in reducing insulin resistance and in normalization of ALT in patients with NAFLD (13–20). However, only a few studies have evaluated histological improvement in NAFLD based on biopsy results (14,19,20).

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Table 1.
Diet Trials in NAFLD

- Daily 600–800 calorie intake reduction (13)
- Restriction of caloric intake to <25 kcals/kg/day of ideal body weight (14)
- Restriction of total dietary fat content to <30% of the caloric intake with <10% of the caloric intake from saturated fats (15,16,17)
- Restriction of caloric intake to <30 kcals/kg/day (18)
- Low calorie/low carbohydrate (40–45% of caloric intake) (19)

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Different diets have all documented a normalization of the ALT levels 1–3 months after initiation of dietary changes (see Table 1). At least three studies on weight loss in NAFLD patients (14,19,20) have documented histologic improvement in steatosis and inflammation with biopsies, including one in children (20). Studies comparing the efficacy of different types of diets (i.e., traditional low fat vs. calorie restriction with low carbohydrate diet) in producing weight loss have not been able to prove the superiority of one over the other. However, none of these studies have looked at NAFLD as an endpoint (21–23).

Of interest, all studies support the fact that even small degrees of weight loss of around 5–10% of the total body weight show a clear benefit. This seems to indicate that changes in the amount of fat delivery to the liver related to dietary fats and the subsequent alterations in lipid metabolism are as important as the actual weight loss (19). This would be an important point for clinicians to emphasize to NAFLD patients during weight loss counseling, as the weight loss itself is just one of the goals of the intervention.

There is concern that very rapid weight loss (generally >1.6 kg/week) may cause worsening of the inflammation with NASH, and thereby accelerate progression of the disease by drastically increasing visceral adipose tissue breakdown and delivery to the liver (24).

All of the above studies combined dietary changes with aerobic exercise in varying intervals and varying levels of supervision. No studies looking at exercise alone without the confounding effect of weight loss have been reported.

ROLE OF ORLISTAT IN AUGMENTING WEIGHT LOSS IN NAFLD PATIENTS:

Orlistat is an inhibitor of gastric and pancreatic lipase, which reduces the absorption of long chain fatty acids and cholesterol by approximately 30%, with the unabsorbed fat excreted in the stool. Four published studies have shown the benefit of adding orlistat in obese patients with NAFLD (25–28). A double blind, placebo controlled study with 44 patients randomized to either receive orlistat 120 mg thrice daily or placebo for six months, with all patients undergoing a similar

weight reduction program, showed that a higher percentage of patients receiving orlistat with reduced ALT levels (48% in orlistat group vs. 26% in placebo). There was a statistically significant reduction in fatty liver by ultrasound in the orlistat group compared to placebo. This was despite a similar reduction in BMI in both groups (28).

In the largest meta-analysis looking at the use of orlistat in obese patients, a total of 16 clinical trials with 10,631 patients were identified (29). Orlistat improved blood pressure and glycemic control, decreased LDL and total cholesterol levels, and reduced the incidence of diabetes, and produced a mean weight reduction of 2.9 kg compared to the placebo group when followed for one year (29). However, NAFLD was not specifically assessed in these trials.

Orlistat should therefore be considered in obese patients with NAFLD, particularly when they fail to lose weight, despite an adequate program of nutritional counseling and exercise.

ANTIOXIDANTS IN NAFLD

A recently published Cochrane database meta-analysis looked at six trials which used a combination of different antioxidants including selenium, vitamin C and vitamin E to evaluate their effects on the progression of NAFLD. It concluded that there was insufficient evidence to support or refute a role for these in NAFLD patients (30). Another recently published study looked at the effects of lifestyle changes and weight loss with or without the use of vitamin C and E in 53 children with NAFLD. The authors showed that a mean weight loss of around 4.7 kg produced significant histologic improvement in the degree of steatosis, lobular inflammation and ballooning degeneration in hepatocytes as determined by a liver biopsy at 24 months of treatment. The study showed no additional effect of using vitamin C or E over weight loss alone (20).

Betaine is a methyl group donor which increases the hepatic S-adenosyl-methionine levels and thereby may help combat oxidative stress in the liver. A recent randomized controlled trial looking at the effect of daily betaine supplementation in patients with NASH failed to show a clear benefit (31).

n-3 POLYUNSATURATED FATTY ACIDS (n-3 PUFA) AND NAFLD

Animal studies have shown that n-3 PUFA enriched diets reduce hepatic triglyceride content and the development of steatohepatitis (45). The benefit is thought to be due to the modulation of lipid processing by n-3 PUFA's by acting as ligands of the peroxisome proliferator-activated receptor α (PPAR α) and reducing hepatic inflammation and oxidative stress (32).

The first clinical trial studying the role of n-3 PUFA in NAFLD was published in 2006 by Capanni et al (33). Both biochemical (ALT, GGT) and ultrasound improvement in NAFLD was shown in the 42 patients who received 1 gm n-3 PUFA daily over a period of 12 months. Another larger study evaluated a total of 134 patients randomized to a control group (which received a calorie restricted diet and placebo) and a study group (which received the recommended diet and 2 gm thrice daily of n-3 PUFA). The authors showed a 53% reduction in fatty liver in those patients receiving n-3 PUFA compared to 35% in patients receiving dietary management alone (34). Similar biochemical and imaging improvement in NAFLD was seen in two more studies using n-3 PUFA (35,36). No adverse events were reported in any of these studies. n-3 PUFA may have a role in the management of NAFLD, but more studies are needed to confirm its benefit and define dosing and duration of administration.

HIGH FRUCTOSE CORN SYRUP AND TRANS-FATTY ACIDS IN NAFLD

High fructose corn syrup (HFCS) is a common sweetener in soft drinks and fruit drinks. Currently the average American consumes 12% of the total energy intake as fructose, primarily as HFCS (38). Porikos et al showed transaminase elevations in healthy people consuming 25% of their calories in the form of sucrose which contains 50% fructose (37). A recent study comparing the dietary patterns of 49 patients with NAFLD to 24 control patients with other types of chronic liver disease, found a two fold higher consumption of HFCS in patients with NAFLD (365 kcal vs. 170 kcal) (39). Another crossover study with 16 healthy males (with history of diabetes in parents) and 8 controls who received either a high calorie and high fructose diet or a

Table 2.

Practical Recommendations for Management of NAFLD

1. Nutritional counseling and appropriate follow-up with a dietitian is the first line of therapy with specific emphasis on the role of daily exercise/activity.
2. Walking or some form of daily aerobic exercise at least 30–45 minutes daily is encouraged.
3. No clear evidence to recommend the traditional low fat vs. the newer high fat, low carbohydrate diets.
4. Losing even 5–10% of total body weight can be sufficient to create a significant improvement in NAFLD and metabolic syndrome in general.
5. Avoid excessively rapid weight loss (>1.6 kg/week), as it may increase the progression of NAFLD.
6. Careful attention to the management of the accompanying metabolic syndrome—hyperlipidemia, heart disease, diabetes.
7. Morbidly obese patients (BMI >40 or BMI >35 with co-morbidities) should be considered for referral for bariatric surgery.
8. n-3 PUFA appear to be encouraging as potential treatment for NAFLD, but further studies are needed to support this.
9. Trial of orlistat in patients failing diet therapy.
10. Avoid foods with HFCS and trans-fats.

isocaloric diet for 7 days, showed an increase in hepatic fat deposition as assessed by MR spectroscopy (40).

Trans-fatty acids (TFA) have been shown to be associated with obesity, insulin resistance and coronary artery disease (41). Animal studies have documented the role of TFA in the pathogenesis of NAFLD and NASH (42,43). However, no human studies looking at the association of NAFLD and trans-fats have been completed so far.

ROLE OF BARIATRIC SURGERY IN PATIENTS WITH NAFLD

The most studied intervention in obese patients for weight loss is the use of bariatric surgery. The National Institutes of Health (NIH) guidelines recommend bariatric surgery for obese patients with a BMI >40 kg/m² or >35 kg/m² for patients with significant co-morbidities such as heart disease, diabetes or obstructive

tive sleep apnea (44). Currently, the common bariatric surgical procedure is the Roux-en-Y gastric bypass (RYGB). A recent large meta-analysis of the effect of bariatric surgery on NAFLD and NASH included 15 studies with 766 total paired liver biopsies. A significant improvement in steatosis was observed in 91%; steatohepatitis improved in 81%; and fibrosis improved in 65% of the patients (45). This is in addition to the already well documented salutary effect of bariatric surgery on reducing mortality and morbidity from cardiovascular disease and diabetes (46). Approximately 1–3% of patients undergoing bariatric surgery already have cirrhosis (47). Patients with advanced fibrosis or compensated cirrhosis may also receive some benefit from bariatric surgery, but there is also a significant risk of decompensation with the surgery (48). Bariatric surgery as an option has not been studied in patients with NASH or fibrosis who do not have a BMI >40 (or >35 with co-morbidities). More data will be needed prior to making a recommendation for surgical intervention in this group of patients.

CONCLUSIONS

NAFLD represents the most common cause of chronic liver disease in the developed world. Progression of benign steatosis to steatohepatitis, and finally, cirrhosis makes it likely to emerge as the major cause of liver disease related mortality in the next decade. Unfortunately, drug therapy for NAFLD is not currently available and management must focus on treatment of the “metabolic syndrome” rather than NAFLD as an individual entity. This entails an important challenge in educating clinicians in the recognition of this disease and initiation of appropriate interventions targeted at weight loss in close consultation with a dietitian. There is enough evidence documenting the salutary effect of weight loss in not only reducing the steatosis and inflammation, but also in some cases reversing the fibrosis seen with advanced disease. Patients who do not respond well to targeted nutritional intervention can be candidates for using orlistat to augment weight loss. The use of n-3 PUFA is emerging as an encouraging new treatment adjunct. Patients who meet criteria for bariatric surgery should be appropriately referred for such procedures. ■

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