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AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review

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Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease, with global public health impact affecting more than 25% of the global population. NAFLD is associated with significant morbidity and mortality from cirrhosis, hepatocellular carcinoma, solid organ malignancies, diabetes mellitus, cardiovascular disease, and obstructive sleep apnea, resulting in significant health care resource use and decreased health-related quality of life. NAFLD cirrhosis is a leading indication for liver transplantation in the United States. Lifestyle modification to achieve weight loss remains a first-line intervention in patients with NAFLD. We summarize evidence-based interventions for lifestyle modification in the treatment of NAFLD and provided best practice advice statements to address key issues in clinical management.

Keywords: Fatty Liver; Steatohepatitis; NASH; Weight Loss; Exercise; Diet; Liver Fibrosis; Obesity; Cirrhosis.

BEST PRACTICE ADVICE STATEMENTS

Best Practice Advice 1: Lifestyle modification using diet and exercise to achieve weight loss is beneficial for all patients with nonalcoholic fatty liver disease (NAFLD).

Best Practice Advice 2: Among patients with nonalcoholic steatohepatitis, weight loss $\geq$5% of total body weight can decrease hepatic steatosis, weight loss $\geq$7% of total body weight can lead to nonalcoholic steatohepatitis resolution, and weight loss $\geq$10% of total body weight can result in fibrosis regression or stability.

Best Practice Advice 3: Clinically significant weight loss generally requires a hypocaloric diet targeting 1200–1500 kcal/d or a reduction of 500–1000 kcal/d from baseline.

Best Practice Advice 4: Adults with NAFLD should follow the Mediterranean diet, minimize saturated fatty acid intake specifically red and processed meat, as well as limit or eliminate consumption of commercially produced fructose.

Best Practice Advice 5: A hypocaloric diet should be implemented for patients with lean NAFLD (body mass index 26 kg/m^2 non-Asian or body mass index 24 kg/m^2 Asian) with a lower target weight-loss threshold of 3%–5%, as they experience similar histologic benefits for steatosis and nonalcoholic steatohepatitis as patients with overweight or obese NAFLD.

Best Practice Advice 6: The effect of other specific hypocaloric diets, such as low-carbohydrate/high-protein diets, meal replacement protocols, intermittent fasting, and vitamin supplementation, on histologic NAFLD end points have not been studied adequately to support their routine use in NAFLD-specific treatment.

Best Practice Advice 7: Regular physical activity should be considered for patients with NAFLD, with a target of 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic exercise per week. Resistance training exercise can be complementary to aerobic exercise and can have independent effects on NAFLD. The impact of exercise on NAFLD can enhance the positive effect of hypocaloric diet.

Best Practice Advice 8: Patients with NAFLD should be evaluated for coexisting metabolic conditions, such as obesity, diabetes mellitus, hypertension, dyslipidemia, and cardiovascular disease. These comorbidities should be managed aggressively.

Best Practice Advice 9: Alcohol consumption should be restricted or eliminated from the diets of adults with NAFLD.

Best Practice Advice 10: Sarcopenia is commonly observed in patients with nonalcoholic steatohepatitis cirrhosis. This group might require specialized dietary and activity management.

Nonalcoholic fatty liver disease (NAFLD), a metabolically derangement-based liver disease, is a leading cause of chronic liver disease with global public health impact affecting more than 25% of the global population.[1] This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of Gastroenterology. Among those with NAFLD, it is estimated that 1 in 4 might have nonalcoholic steatohepatitis (NASH). NASH is associated with significant morbidity and mortality due to complications from

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Abbreviations used in this paper: AGA, America Gastroenterological Association; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; ILI, intensive lifestyle intervention; Med, Mediterranean; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TBW, total body weight.

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cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC).[2,3] In the context of the rising incidence and prevalence of NAFLD in tandem with obesity and metabolic syndrome, NAFLD-associated cirrhosis and HCC are expected to emerge as leading indications for liver transplantation within the next decade.[4] In addition, patients with NAFLD are also at higher risk of developing nonhepatic solid cancers.[5] NAFLD is also related to increased mortality as a result of cardiovascular disease (CVD), diabetes mellitus, and lung disease to include obstructive sleep apnea.[6] Finally, NAFLD is not restricted to patients with obesity, as recent studies have confirmed that the prevalence of normal-weight NAFLD in the general population can range from 4% to 10%. However, within the NAFLD population, up to 40% can be considered to be of normal weight, depending on the number of metabolic derangements present.[7–10] Normal-weight NAFLD can carry a high morbidity and mortality burden.[7,8]

Lifestyle modification, including significant weight loss through hypocaloric diet and exercise, is considered as a first-line intervention for the treatment of NAFLD, as weight loss is associated with a reduction in liver fat, which provides potential for reversal of disease progression.[11,12] As such, the American Association of Gastroenterology provided guidance on how to manage obesity care for safe and effective weight management. The guidance centers on 4 guiding principles (ie, assessment, intensive weight-loss intervention, weight stabilization and re-intensification if needed, and prevention of weight regain) obtained through a reduced-calorie diet, physical activity, medications, bariatric endoscopy, and surgery to achieve weight loss.[13] However, medications, bariatric endoscopy, and surgery to achieve weight loss are largely focused on subsets of patients with severe obesity, co-existing diabetes mellitus, and/or biopsy-proven NASH with, at a minimum, stage 2 fibrosis. Therefore, lifestyle modification using diet and exercise to achieve weight loss remains the cornerstone for management of NAFLD.[13]

This review then is designed to provide this guidance on the key clinical issues needed to achieve weight loss through lifestyle modification focused on diet and exercise for patients with NAFLD. We have developed Best Practice Advice (BPA) statements to address 10 key clinical issues. This review has undergone internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*. However, it is important to note that these guidance statements require a team approach to improve adherence, such that the use of personnel educated in diet and in exercise should be incorporated so that each patient's diet and exercise plan can be individualized to be culturally sensitive, socially appropriate, obtainable, and measurable.[14]

Best Practice Advice 1: Lifestyle modification using diet and exercise to achieve weight loss is beneficial for all patients with NAFLD.

Lifestyle modification centered on diet and physical activity (as described in detail below) to achieve weight loss as well as the avoidance of alcohol are the foundations of treatment for all patients with NAFLD, regardless of histologic type. NAFLD is a risk factor for diabetes mellitus, CVD, and cancer both liver and non–liver-related. The reduction of body weight results in decreased liver fat and improved glucose control/insulin sensitivity reducing the risks for diabetes mellitus, CVD, as well as decreasing the risks of progressive liver disease (discussed below).[1,11,12,15,16] Research is needed to determine the impact of weight loss, NAFLD, and the development of uterus, stomach, pancreas, and colon cancers.

Best Practice Advice 2: Among patients with NASH, weight loss of ≥5% total body weight (TBW) can decrease hepatic steatosis, weight loss of ≥7% TBW can lead to NASH resolution, and weight loss of ≥10% TBW can result in fibrosis regression/stability.

Weight loss improves multiple facets of NAFLD histology. A randomized controlled trial compared 48 weeks of an intensive lifestyle intervention (ILI), including caloric reduction and physical activity to standard structured education on weight loss and NASH histology. Although the control had no significant change in weight, the ILI group lost, on average, 9.3% TBW. Participants with ≥7% TBW loss had significant improvement in steatosis, lobular inflammation, hepatocyte ballooning, and NAFLD activity score, although no change in fibrosis was seen. A second prospective cohort examined the impact of higher degrees of weight loss on histology and found that after 1 year of ILI among those who achieved a 5%–6.99% TBW loss, 65% had improvement in steatosis.[17] Among those who achieved a 7%–8.99% TBW loss, 64% had NASH resolution, and among those with ≥10% TBW loss, 45% had fibrosis regression of at least 1 stage, and the remaining 55% had fibrosis stabilization.[17] These findings demonstrate that weight loss can significantly impact all aspects of NAFLD histology, including fibrosis, but a goal of 10% TBW loss should be considered for patients with overweight or obese NAFLD. In addition to this pivotal trial, several systematic reviews and meta-analyses have reported similar findings on diet and exercise, highlighting that the more intensive the weight-loss intervention, the more weight loss occurs, which can lead to improved NAFLD-related liver biomarkers.[18–20]

Best Practice Advice 3: Clinically significant weight loss generally requires a hypocaloric diet targeting 1200–1500 kcal/d or a reduction of 500–1000 kcal/d from baseline.

Hypocaloric diets are an important component in the treatment of NAFLD. Hypocaloric diets are characterized by a decrease in daily caloric intake by 500–1000 kcal/d or to a target of 1200 kcal/d for women and 1400–1500 kcal/d for men. Hypocaloric diets are associated with weight loss as well as improvements in insulin resistance and decreases in liver enzymes and intrahepatic fat.[5,6] The improvements in intrahepatic fat following a hypocaloric diet can persist even with weight regain 2 years after weight loss.[8] However, data are lacking as to the long-term effect of very low hypocaloric diets (approximately 800 kcal/d) in those with NAFLD, although 1 small study reported reversal of NAFLD by day 28 on 800 kcal/d among women with obesity.[21]

Best Practice Advice 4: Adults with NAFLD should follow the Mediterranean (Med) diet or a diet of similar design and minimize saturated fatty acid intake, specifically red and processed meat, and commercially produced fructose consumption.

Several diets may be appropriate for weight loss in those with NAFLD[22–24]; however, the Med diet has been the most studied for those with NAFLD/NASH and is thought to reduce the risk of and progression of NAFLD through the nutraceutical effect of bioactive compounds and phytochemicals with their antioxidant and anti-inflammatory capacity associated with the ingestion of certain fibers, monounsaturated and omega-3 fatty acids, and phytosterols found in the Med diet.[25,26]

The Med Diet is characterized by daily consumption of fresh vegetables, fruit, legumes, minimally processed whole grains, and fish, along with omega-3-fatty acids, such as olive oil, nuts, and seeds as the primary fat sources, with minimal to low consumption of diary and red and processed meat.[27] The Med diet is beneficial in the prevention and treatment of multiple metabolic conditions, including CVD and diabetes mellitus and is associated with a decrease in overall mortality.[28] Among adults with NAFLD, the Med diet, even in the absence of weight loss, leads to a reduction in hepatic steatosis with an increase in insulin sensitivity compared with a low-fat, high-carbohydrate diet.[28] A recent study from the Framingham Heart Study found that for every standard deviation increase in the Mediterranean Diet Score (a measure of Med diet consumption) the odds for incident fatty liver decreased by 26%. An increased Mediterranean Diet Score was also found to be associated with reduced liver fat accumulation and severity.[29]

Foods rich in saturated fatty acids, such as meat, are associated with both CVD and diabetes mellitus.[30] Total meat consumption ($\geq$1.1 portions/d or $\geq$7.7 portions/wk), red meat ($\geq$0.33 portions/d or $\geq$2.3 portions/wk), and processed meat ($\geq$0.10 portions/d or $\geq$0.7 portions/wk) are associated with NAFLD and should be limited.[31] Although the impact on NAFLD of eliminating meat from the diet has not yet been evaluated, limiting overall meat intake and avoidance of processed meats in patients with NAFLD should be considered.

Increased consumption of fructose, predominantly high-fructose corn syrup in sugar-sweetened beverages, is associated with postprandial hypertriglyceridemia and visceral adiposity contributing to insulin resistance and NAFLD.[32,33] Among adults with NAFLD, fructose consumption, quantified by consumption of sugar-sweetened beverage, is associated with higher fibrosis stages. Furthermore, among older adults, fructose consumption is associated with increased hepatic inflammation and hepatocellular ballooning.[33] However, fructose contained in fruits is not associated with NAFLD, so fruit consumption should not be restricted.[34]

Best Practice Advice 5: A hypocaloric diet should be considered as treatment for patients with normal-weight NAFLD (body mass index ≤25 kg/m^2 in non-Asian or body mass index ≤23 kg/m^2 in Asian patients) with a lower target weight-loss threshold of 3%–5%, as they experience similar histologic benefits for steatosis and NASH as patients with overweight or obese NAFLD.

Patients considered to be of normal weight have NAFLD and the severity depends on the metabolic derangements present. However, there is little published on the management of normal-weight NAFLD, although the few published studies have suggested that those with normal-weight NAFLD can significantly benefit from ILI and weight loss through improvement of hepatic fat, decreased waist circumference, and decreased low-density lipoprotein levels. Similar to patients with obesity and NAFLD, a reduction of body weight and remission of NAFLD is dose-dependent for those with normal-weight NAFLD. In adults with normal-weight NAFLD, a 3%–5% TBW loss can also result in NAFLD resolution in 50% and a 7%–10% TBW loss results in resolution of NAFLD in 70%.[35,36] Liver stiffness assessed by transient elastography also improved in patients with normal-weight NAFLD who participated in the lifestyle intervention compared with those in the control arm.[35] The durability of weight loss and the impact of weight regain in normal-weight NAFLD is not known.

Best Practice Advice 6: The effect of specific hypocaloric diets, such as low-carbohydrate/high-protein diets, meal-replacement protocols, intermittent fasting, and vitamin supplementation, on histologic NAFLD/NASH end points have not been adequately studied; however, there are potential benefits of certain hypocaloric diets to treat patients with NAFLD, which require an individual approach before prescribing.

Studies of meal-replacement diets for the treatment of NAFLD have been limited by small size and have failed to demonstrate a benefit in NAFLD. Intermittent fasting, also known as time-restricted eating, limits the hours or days that calories are consumed and should be individualized. A study of alternate-day fasting in adults with NAFLD led to weight loss and improvement in lipid parameters, but no change in liver stiffness by transient elastography.[37] A second study of intermittent fasting was associated with a reduction in the fatty liver index in adults with and without diabetes mellitus.[15] Both studies are limited by lack of radiographic or histologic end points and additional studies are needed before intermittent fasting can be routinely considered for the treatment of NAFLD.

Low-carbohydrate, high-protein diets have been studied for weight loss in obesity, but limited data exist in NAFLD.[38,39] A single study found that a low-carbohydrate, high-protein diet resulted in weight loss and improvement in liver enzymes, but no data on radiographic or histologic improvement was ascertained.[38] A second study evaluated the impact of a low-carbohydrate diet and a high-carbohydrate diet on intrahepatic triglyceride content and found that, at 48 hours, those on the low-carbohydrate diet had significantly greater decreases in intrahepatic triglyceride, but after 11 weeks there was no difference by diet on intrahepatic triglyceride content.[15] Thus, a high-protein, low-carbohydrate diet cannot yet be considered as the preferred diet for the treatment of NAFLD. Patients should

be counseled to follow a Med diet as above and modulate the carbohydrate and protein content that best suits them.

Vitamin E, based on the results of the PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis) trial, is currently recommended as a treatment for biopsy-proven NASH in adults without diabetes. However, while vitamin E improved several aspects of NASH histology, it had no benefit on fibrosis, which is the only variable associated with mortality. Furthermore, vitamin E may be associated with increased risks of prostate cancer and all-cause mortality, limiting its use. Similarly, vitamin C in high doses can impact several aspects of NASH histology, but results have been conflicting regarding the impact of vitamin C on fibrosis and further evaluation is needed before it can be considered for routine use.[40]

Best Practice Advice 7: Regular physical activity should be considered to patients with NAFLD with a target of 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic exercise per week. Resistance training can be complementary to aerobic exercise but not a replacement.

Exercise's impact on NAFLD can enhance the positive effect of hypocaloric diet. Physical activity, independent of weight loss, can improve NAFLD by reducing hepatic fat content, in part by improving the body's peripheral sensitivity to insulin, decreasing hepatic de novo lipogenesis, decreasing adipocyte lipolysis, and reducing free fatty acid delivery to the liver.[36,41] Physical activity can be accomplished through aerobic activity, such as walking or stationary biking, while resistance training is accomplished with load-lifting exercises, such as weight training using a weight machine. A systemic review and meta-analysis assessing the impact of exercise on NAFLD found that exercise alone (predominantly aerobic exercise), without dietary intervention, significantly decreased liver fat with a nonsignificant trend toward improvement in alanine aminotransferase compared with control groups.[36] Individual studies have varied by aerobic exercise type and duration; however, benefits for steatosis were seen with 90–300 minutes per week. As such, in general, 150–300 minutes of moderate-intensity exercise (3–6 metabolic equivalents) or 75–150 minutes of vigorous-intensity exercise (more than 6 metabolic equivalents) should be considered for patients.[41]

Resistance training has been shown to decrease steatosis with lower intensity than aerobic exercise and can be an option for those with limited aerobic capacity; however, in a most recent population-based study, walking more than 3 hours per week was associated with decreased cirrhosis-related deaths and HCC, so encouragement for aerobic activity should be considered.[41,42] It is important to note that exercise seems to enhance the weight-reduction benefit of diet so moderate physical activity in conjunction with the Med diet might be associated with the most weight loss, as well as reduction in visceral adipose tissue and percent intrahepatic fat.[34–36,41]

Best Practice Advice 8: Patients with NAFLD should be evaluated for co-existing metabolic conditions, such as obesity, diabetes mellitus, hypertension, dyslipidemia, CVD, and obstructive sleep apnea. These comorbidities should be managed aggressively.

The presence of co-existing metabolic conditions in those with NAFLD and NASH is high. In a recent meta-analysis on the global burden of NAFLD, investigators reported the pooled overall prevalence estimates of obesity, diabetes, hyperlipidemia, hypertriglyceridemia, hypertension, and metabolic syndrome among NAFLD and NASH patients (Table 1), so practitioners should have a high index of suspicion when evaluating patients.[1] Obstructive sleep apnea is also a common comorbidity associated with higher morbidity and mortality, so further investigation for obstructive sleep apnea may be warranted.[43]

Because these comorbidities are also associated with development of CVD, CVD remains one of the major causes of death among those with NAFLD and or NASH and, as such, patients with NAFLD and NASH with these comorbidities should be referred for further evaluation of cardiovascular health.[44] Therefore, we suggest that all those with NAFLD and co-existing metabolic conditions, such as obesity, diabetes mellitus, hypertension, and hyperlipidemia, be risk-stratified for CVD and treated as per American College of Cardiology/American Heart Association guidelines in addition to the weight-management strategies, as fully described in the AGA POWER (Practice Guide on Obesity and Weight Management, Education, and Resources) program.[13,22,45]

Best Practice Advice 9: Alcohol consumption should be restricted in the diets of adults with NAFLD.

Conflicting data exist on the contribution of alcohol consumption to the development and progression of NAFLD. Cross-sectional studies suggested that low to moderate alcohol use is associated with decreased odds of NASH, hepatocyte ballooning, and fibrosis in NAFLD. However, studies have been limited by their cross-sectional nature and inability to establish causality. A recent large prospective study of alcohol and NAFLD has provided important evidence that alcohol use, even at low levels, is associated with increased liver-related outcomes in those with NAFLD. This study, which evaluated 8345 with NAFLD (fatty liver index >60), found that after a mean follow-up of 11.1 years,

Table 1. Prevalence of Selected Comorbidities in Patients With Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Comorbidity	NAFLD, %	NASH, %
Obesity	51.3	81.8
Type 2 diabetes mellitus	22.5	43.6
Dyslipidemia	69.2	72.1
Hypertriglyceridemia	40.7	83.3
Hypertension	39.3	68.0
Metabolic Syndrome	42.5	70.7

NOTE. From Younossi et al,[1] adapted with permission.

9–20 g of daily general alcohol use or 0–9 g of daily non-wine alcohol use doubled the risk for adverse liver-related outcomes compared with lifetime abstainers. Only among never smokers was alcohol use (up to 49 g daily) associated with a decreased risk of cardiovascular events and death.[46] Therefore, adults with NAFLD should restrict alcohol consumption to reduce liver-related events and smokers (current or prior) should avoid alcohol entirely.

Best Practice Advice 10: Sarcopenia is commonly observed in patients with NASH cirrhosis. This group can require specialized dietary and activity management.

Sarcopenic obesity (low muscle mass in the presence of obesity) in cirrhosis is associated with poor clinical outcomes, including increased mortality. A recent study found that among patients with cirrhosis who were on the waiting list for liver transplantation, 59% had sarcopenia. Investigators found that obesity and age were independently associated with pretransplantation sarcopenia, while NASH as an etiology of cirrhosis was also an independent predictor of sarcopenic obesity. In fact, those with NASH cirrhosis were 6 times more likely to have sarcopenic obesity. In this context, it is important to address sarcopenia in patients with NASH.

During the past decade, there has been substantial research to better understand the underlying mechanisms of sarcopenia in cirrhosis. In this context, it is believed that the inability of the cirrhotic liver to store, synthesize, and mobilize carbohydrates causes patients to rapidly transition to a catabolic state in which protein and fat are used as energy sources. This imbalance between protein synthesis and muscle tissue breakdown, increased autophagy and proteasomal activity, and impaired mitochondrial function in cirrhotic patients, independently contribute to the development of sarcopenia. To avoid caloric deficits, an individualized dietary plan should be devised to meet required caloric and nutritional requirements.[47] In this context, the minimum protein intake of 1.2–1.5 g/kg, with branched-chain amino acids obtained from protein sources such as chicken, fish, eggs, nuts, lentils, and/or soy, should be considered.[47] Patients should be encouraged to eat frequent small meals and avoid more than 4–6 hours between meals. As such, a bedtime snack containing protein and at least 50 g of complex carbohydrates should be considered. Given the complexity of the nutritional needs of this group, consultation with a specialized nutritionist is preferred.[47] In addition to dietary changes, moderate-intensity exercise can be beneficial, ideally for a duration of 150 minutes per week.[47] In summary, given the high prevalence of sarcopenia in cirrhosis and its impact on long-term outcomes, further research to characterize the mechanisms of sarcopenia and elucidate targets for novel therapy are needed.

Conclusions

Lifestyle modifications, which include diet and physical activity to achieve weight loss, are the cornerstone of treatment for NAFLD. Additionally, restriction or elimination of alcohol consumption and optimal management of cardiometabolic comorbidities are also highly important. In this expert review, we provide practical advice through 10 Best Practice Advice statements to help practitioners in their development of a treatment plan for their patients with NAFLD to include treatment of sarcopenia in NASH cirrhosis.

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Conflicts of interest
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