

**LAUREN VAN DAM:** I'll be covering the nutritional management and counseling recommendations for patients with NAFLD. And as Dr. Glass alluded to, weight loss is very important. And really, the cornerstones for NAFLD therapy are weight loss, diet modification, and exercise. And so I'll be going into a little bit more detail on the supporting research for each of these interventions as well as some considerations for recommendations for your patients in practice.

Dr. Glass did touch on this study a little bit. It's one of the key studies looking at weight loss in patients with NASH. And it was a one year intervention, a large study with 293 patients with NAFLD. And a third of them had diabetes as well as 2/3, about, with metabolic syndrome. So there's that correlation, again, as Dr. Glass mentioned.

NAFLD is the liver manifestation of metabolic syndrome, essentially. 40% of the patients had fibrosis, but only 11% had stage 3 fibrosis. So there were more mild cases included in this study. And the intervention included a hypocaloric diet, so they prescribed a 750 calorie per day deficit below basal energy expenditure as estimated by the Mifflin-St. Jeor equation.

Looking at the diet recall data, the actual average reduction was only about 400 calories per day from their baseline intake, however. Their exercise recommendations included working up to walking 200 minutes per week, and they were encouraged to do this over the course of about six months and divided into about five sessions per week. And they also saw a dietitian every eight weeks at baseline and throughout the one year study. This was individual, one-on-one counseling as well as the group setting.

And the patients were encouraged to follow a low fat diet with about average protein intake and at least 20 grams of fiber. And so they were just given healthy eating guidelines, including increased fruit and vegetable and whole grain consumption. And they were asked to complete three-day diet records as well as exercise records to measure compliance.

Also, the glitazones and vitamin E were prohibited during this study. As you saw with Dr. Glass' presentation, that these are suggested to have a decrease in NASH. So what they found was a significant correlation between total body weight loss and total resolution of NASH. They took baseline biopsies. And then again at one year for the patients who lost more than 5% of their total body weight, 58% had complete resolution of their NASH.

Dr. Glass also mentioned that 82% of this group were able to decrease their NAFLD activity score by two points, so even modest weight loss had an effect on their disease. And then in the patients who were able to lose at least 10% of their body weight, 90% had resolution of NASH as well as 45% decrease in fibrosis. And you can see in the graph, there was a good correlation between those with a higher percent of total body weight loss and resolution of their NASH. So good data to suggest that a weight loss intervention is effective in both reducing the degree of NASH as well as possibly fibrosis at higher weight loss.

Another study by our own Dr. Glass was a retrospective cohort with 45 patients. And these were patients with fibrosis, and what they did was measure fibrosis at baseline as well as at follow-up. The average follow-up was about 4 and 1/2 years later. And they found that the patients who lost the most weight, so greater than 10% of their body weight, had decrease in fibrosis, so again, reiterating what the other studies found.

And so the chart shows the fibrosis score at baseline and the follow-up biopsies. So you can see in the first column, greater than 10% body weight loss. There is the decrease in fibrosis score. The middle column shows 0% to 10% weight loss. And these patients, essentially, had stable fibrosis. And then in the last column, patients who gained weight had progression of their fibrosis.

Interestingly, 12 of these patients had bariatric surgery. And of those 12, about 63% achieved fibrosis regression versus only 9% in those who did not have bariatric surgery, likely because of the amount of weight loss achieved with the bariatric procedure. So as far as the clinical practice guidelines, there is enough data to suggest that 3% to 5% weight loss can reverse simple steatosis.

Greater weight losses but still modest amounts at 5% to 7% weight loss can reverse steatosis and even inflammation. And then really, to reverse fibrosis, greater than 10% weight loss is needed to achieve that. And so those can be good initial goals to set with your patients. Of course, for a long term goal, maintaining the weight loss that has already been achieved is extremely important.

So continuing to work with the patient and helping them maintain this healthy lifestyle and their goal weight as well as, if necessary, working towards continued weight loss gradually over time towards their ideal body weight or healthy BMI, if appropriate. To achieve this weight loss, it's suggested a calorie reduction of 500 to 750 calories below their basal energy expenditure for slow, gradual weight loss of about one to two pounds per week.

And a maintainable diet that is realistic for the patient for sustained weight loss is really key, and so the best approach, of course, varies from person to person. And so various methods might include Weight Watchers, some patients like to journal their intake and use my MyFitnessPal to track their progress, individual versus group counseling sessions. And then as far as diet composition in the setting of calorie reduction, if the goal is weight loss, all of them can work.

However, some recent research has been looking at specific diet composition and how that affects the liver and NAFLD. And so that's our next section here is diet composition. The goals of dietary modification should be really to improve metabolic alterations, including insulin resistance and dyslipidemia, and also to specifically reduce hepatic steatosis, inflammation, and fibrosis. As well as looking at their comorbidities that they're at risk for, including cardiovascular disease and diabetes and, of course, to support and maintain their weight loss efforts.

So the initial data looking at the Mediterranean style diet seems to fit the bill because of the known benefits for cardiovascular disease, diabetes, and metabolic syndrome. And so we'll look a little bit at the data for that. But other research has also looked at intake of fructose, the low carb diets, high fat diets, high protein diets, vitamin E and antioxidants, even coffee, tea intake and alcohol and omega 3 fatty acids. So I'll highlight a couple pieces of research related to those topics.

So looking at risk factors for NAFLD and diet, the Western dietary patterns, as you can imagine, pose a significant risk for this population. And that's because the Western dietary patterns are associated with weight gain, insulin resistance, and obesity. And the key features of the Western dietary patterns, high sugar consumption-- especially with high fructose corn syrup in sugary drinks-- refined grains rather than whole grains and low overall fiber intake, high saturated fat and trans fat intake with processed meats, fast food, and convenience meals as well as red meats.

And going along with that, high salt consumption with more meals away from home and, generally, low intakes of fruits and vegetables, which translates to low antioxidant intake. And to make everything worse, a sedentary lifestyle and poor sleep quality and duration. So this lifestyle pattern seems to be a risk factor for NAFLD, and especially with intake of fructose.

And so if you look at the trends of fructose consumption, obesity, and NAFLD, they all seem to be increasing. And from the "2008 NHANES Survey," they showed that fructose makes up about 10.2% of Americans' calories as of 2008, and that's up from 8% in 1977. And the main sources of fructose that they found in the diet were sugary drinks with high fructose corn syrup at 31% and then grains including processed baked goods at 21%.

The highest intake of fructose was seen in adolescence at age 12 to 18, so really important to-- for those of you, especially, who are working in pediatrics-- to instill good dietary habits early in life in hopes of preventing comorbidities later. So fructose is thought to be steatogenic, because it's metabolized mostly in the liver. And it's associated with increased de novo lipogenesis, dyslipidemia, including elevated triglycerides, liver oxidation-- just oxidation, stress-induced in general, inflammation, and insulin resistance.

So this study I thought was interesting. It looks at different carbohydrate mixtures and the effects of VLDL synthesis and lipogenesis. So there were three different mixtures that they used. The 100 to zero was 100% glucose solution. Then there was a 50-50 glucose-fructose solution and then a 25% glucose, 75% fructose solution.

And these were given in morning boluses, so the first arrow was the morning bolus pointing up at the bottom. And then the second arrow was the standardized lunch. So everyone got the same lunch meal but, of course, they measured the increase in intrahepatic triglycerides, I believe, in lipogenesis after the morning bolus and throughout the day.

And the group that consumed the highest amounts of fructose had an increase in VLDL synthesis in lipogenesis compared to just the glucose-only solution, which is the dark dots at the bottom. And it was pretty close between the 25%, 75% fructose and the 50/50 mixture, actually, in terms of the amount of lipogenesis but just, again, shows that fructose can have detrimental effects, potentially, on the liver.

And even after the standardized lunch, the morning boluses that contained fructose actually promoted lipogenesis after the lunch meal too, so even though all of their lunches were the same. So then getting back to the Mediterranean diet here, which consists of high intakes of olive oil as the main source of added fat, rich in fruits and vegetables, protein sources including legumes, nuts, and seeds, whole grains, plenty of fish and seafood and lean poultry.

The focus is on family meals and home cooking rather than eating away from home and cooking seasonally fresh ingredients. And the intake of red meats and processed meats as well as high fat dairy and added and refined sugars is very low, especially compared to the Western dietary patterns. Also moderate alcohol is part of the Mediterranean way of life. Usually, it's one to two glasses of wine consumed with a meal, so moderation is the key there.

And so the key nutrients that make up the Mediterranean diet are monounsaturated fatty acids, omega 3s. And the Mediterranean diet is usually about 30% to 40% of calories from fat, so not necessarily a low fat diet at all. It's high in fiber and then rich in antioxidants, especially polyphenols and carotenoids. And we all know the benefits of these.

Specifically, they're anti-inflammatory. They can also be antifibrotic and suggested to inhibit denovolyptogenesis. And one of the main source of carotenoids is lycopene, which is rich in tomatoes. And, of course, this is a staple in the Mediterranean diet. So just to take a look at the Mediterranean food pyramid, you might have seen this in the past, but it's fun to take a look back at this.

And they have some specific recommendations, so they categorize it in terms of frequency of how often you should eat these nutrients or foods. And so every main meal they say should include one to two fruits, at least two servings of vegetables and a variety of carbohydrates, mainly from whole grains. And then in the middle category every day, so less of these would be two servings of dairy, olives, nuts, and seeds. So there's your healthy fats.

And then they have some items that they say should be included in the diet weekly like less than two servings of red meat, two to four eggs and then sweets, really, in moderation. And they even have wine on their food pyramid, wine in moderation. So that's a little overview. Essentially, the Mediterranean diet is quite the opposite of the Western diet. And like I said before, the Mediterranean diet has well known benefits for cardiovascular disease, diabetes as well as all-cause mortality.

The liver-specific benefit of the Mediterranean diet, the data is a little bit more limited. But there are a few observational studies and some small randomized trials showing positive results. And in this nice little picture shows the healthy liver and then the Western diet promoting fatty liver and the Mediterranean diet counteracting that via decreased denovolyptogenesis, increased fatty acid beta oxidation and a decrease in insulin resistance, oxidative stress, inflammation, and fibrogenesis.

So a quick look at some of the observational studies that exist on the Mediterranean diet. The first one was the largest study looking at NAFLD patients versus healthy controls. And they use a Mediterranean diet score. And they found that a greater adherence to a Mediterranean diet was a predictor for liver fats severity or lack thereof on ultrasound. So that's just an observational study.

The next one, again, looked at adherence to a Mediterranean diet, and they found a negative correlation with serum ALT, insulin resistance, and severity of steatosis. And those with NASH demonstrated a lower adherence to the Mediterranean diet compared to patients with just simple steatosis. So again, a correlation there.

And then the last one noted, again, greater adherence to a Mediterranean diet associated with lower odds of high grade steatosis and steatohepatitis. A couple randomized trials have been conducted. And the first was an eight week trial, and it looked at high carb, high fiber diet versus a high MUFA diet, which is characteristic of a Mediterranean diet. And these were NAFLD patients with diabetes.

And they found that liver fat reduced more in the group consuming the high MUFA diet compared to the high carb diet, even though weight was stable in both of the groups so independent of weight loss. The next one was a randomized crossover trial so six weeks of Mediterranean diet versus a low fat, high carb diet. And these were non-diabetic NAFLD patients.

Modest weight loss was achieved in both of the diet interventions, but there was a significant reduction in hepatic steatosis on the Mediterranean diet compared to the low fat diet, at 39% compared to just 7%. So some good initial data there. So as far as what you can do in clinic, it appears that the Mediterranean diet as a whole as well as if you look at each of their individual components could potentially be beneficial for liver status.

And it's not an all or nothing intervention, so that means that simple, small changes, making wiser choices could potentially make a difference independent of weight loss. And so the protective effect in NAFLD, because it's independent of weight loss adopting these Mediterranean diet habits, that could be really encouraging for our patients to hear. So maybe they've tried some modifications, and they're following a Mediterranean style diet. But they have not been yet successful in losing weight, and they're becoming frustrated.

That could be encouraging for them to hear, that they're still doing something good for their bodies and helping their liver by just selecting healthier food choices according to Mediterranean principles. And of course, there's the added benefit of the prevention of comorbidities that they're all at risk for, the diabetes, cardiovascular disease, and metabolic syndrome. One study showed that adherence to at least 50% of the Mediterranean diet characteristics was suggested to reduce coronary events so again, not necessarily an all or nothing intervention.

Any change can help. And some tools to consider using to help patients adopt these healthier eating choices could simply just be the healthy plate model. I love to use this in clinic highlighting filling half your plate with veggies so getting more of those antioxidants in fiber rich foods in the diet and just helping them to get a visual and giving them suggestions to fill each portion of that plate there.

You might tell them about the five a day rule as a good goal to increase their total fruit and vegetable intake or even eat your colors since all the different pigments of fruits and vegetables are various antioxidants and polyphenols, which are likely to have a benefit. So as far as coffee and tea intake, good news. There's a meta-analysis that showed an inverse relationship with liver fibrosis and metabolic syndrome with coffee and tea intake.

It's thought to be because of the antioxidant, anti-inflammatory, and antifibrotic effects. And the proposed protective components of the coffee and tea are the polyphenols, such as caffeic acid and ferulic acid in coffee, and the catechins in tea, as well as melanoidins which give coffee its brown color, and then just caffeine in general. So however, further research is needed to confirm the specific liver-related benefit to these and also clarify the dose and optimal type of coffee and/or tea.

As far as alcohol consumption, we know that alcohol has a detrimental effect on the liver. And NAFLD patients, by definition, are not heavy alcohol users. But heavy episodic alcohol consumption at least once per month was associated with fibrosis progression in NAFLD patients and should be discouraged. But similar to cardiovascular disease, it seems like there may be a potential protective effect to moderate alcohol consumption. And so moderation is defined as one drink per day for women and two drinks per day for men.

The NHANES study or survey showed that modest drinkers who consumed up to 10 grams of alcohol per day from wine only had a lower prevalence of suspected NAFLD than nondrinkers. And just for comparison, so 14 grams of alcohol equals about five ounces of wine, so this would be a pretty small glass of wine for 10 grams per day. But so modest wine there is thought to be a protective effect.

And then a cross-sectional study that looked at 251 lifetime nondrinkers versus 330 modest drinkers at one to two drinks per day who had biopsy-proven NAFLD, the modest drinkers had lower odds of having NASH and fibrosis. So more research needed there to confirm but potentially similar to the benefits of cardiovascular disease in moderate alcohol consumption. And then for the NASH-cirrhotic patients, really any regular alcohol consumption can increase the risk of the hepatocellular carcinoma, and so alcohol in this group should be avoided.

As far as other nutrients, so vitamin E, Dr. Glass talked about the study there, so I won't repeat that. But 800 international units per day showed to improve steatosis and inflammation but not fibrosis stage in the NASH patients with biopsy-proven NASH without diabetes. And because this is something that needs to be monitored, it should be administered under the care of a doctor for proper monitoring on that.

And then as far as omega 3 fatty acids, there's really inconsistent data showing a benefit of omega 3 intake or fish oil supplements in NAFLD specifically. So some studies do show a trend towards decrease in liver fat, others show no significant effect. So it's premature to recommend fish oil supplements specifically for NAFLD. However, as part of a Mediterranean diet, it seems reasonable to encourage dietary sources of omega 3 fatty acids because of all of the health benefits in general.

So switching gears to exercise. Dr. Glass mentioned that greater than 50% of NAFLD patients are inactive or sedentary. So this indicates a great opportunity for intervention here. And usually, it's going to be the dietitians who help the patient get started in this if they are in fact sedentary. So aerobic versus anaerobic exercise, both seem to be effective in reducing hepatic fat, which is great because it gives our patients options.

And as far as the data, moderate intensity exercise seems to be able to reduce liver fat, though there may be a dose-dependent response. It doesn't appear that patients need to run marathons in order to help have favorable effects on their liver. So research also has shown that exercise has a positive effect on the liver independent of any weight loss. And so the non-obese NAFLD patients might be likely to benefit from this.

This is just a meta-analysis. There's 16 studies listed here, and the primary outcome was a decrease in intrahepatic lipid content, the primary outcome. And they, overall, showed a favorable effect of exercise versus the control so some mounting evidence here to suggest a benefit for exercise in this group. And then this is an interesting study that looked at the effects of moderate and vigorous exercise on NAFLD so really looking at the intensity.

So it's a 12 month intervention. And the first group was randomized to a vigorous-moderate exercise prescription, so that included 150 minutes per week. And the first six months was jogging at 75% heart rate, and then the last six months was brisk walking at 50% heart rate. And then the other group was just moderate all the way through the 12 months, so brisk walking at 50% heart rate, again, at 150 minutes per week. And then there was a control with no exercise or no change to their normal routine.

And really, there is no difference in liver fat decrease between the moderate and vigorous exercise groups, but there was a significant decrease in liver fat compared to the control. So the bottom graph shows the two intervention groups, the vigorous-moderate and the moderate-moderate. Basically, they almost overlap so no significant difference there. So this is good news that our patients can engage in moderate physical activity. They don't necessarily have to be vigorously exercising in order to have a benefit on their liver.

So some specific recommendations from some of the clinical practice guidelines. For aerobic exercise, really, consistency is key here and in working up to achieving 150 to 200 minutes per week of moderate intensity exercise, ideally, in three to five sessions per week. And that could include brisk walking, stationary bike, maybe the elliptical, or light jogging if they prefer.

And then resistance exercise, again, consistency in duration of the session seems to be important, so it's recommended about 45 minutes per session, three times per week. And again, it's great to give patients options depending on their other health issues. If they have joint pain or if they're not able to engage in cardiovascular exercise, maybe some resistance training might be more appealing to them.

So as I mentioned before, this is a pretty sedentary group, so any increase in activity prior to baseline is likely beneficial. And it's OK to increase gradually, set realistic goals, And maybe that's one day a week that they agree to start with brisk walking for 30 minutes and then gradually working up to something that's maintainable towards the 150 to 200 minutes per week, ideally. The exercise regimen, of course, can be tailored to the patient's preference.

Some patients like to do pedometers and setting goals for a number of steps per day. Group exercise classes or even structured fitness programs can be great for accountability and promoting habitual physical activity as well as peer support. So it's good to figure out which types of resources you're-- if you're at a medical center that they might offer to give some-- and have a discussion with the patient in order to figure out what kind of options they have. If they might join a gym or go to the Y, you can help them kick-start that decision process and how they might get started.

So some key points here. So the lifestyle and diet interventions are focused on improving features of metabolic syndrome, including insulin resistance, decreasing liver steatosis, and prevention in fibrosis, as well as prevention of related comorbidities. And as Dr. Glass mentions, steatosis, inflammation in the liver, as well as fibrosis are all reversible with diet and lifestyle changes, which I think is really great for our patients to hear time and time again.

There is an independent benefit for each of the interventions, weight loss, diet modification, especially following Mediterranean diet principles and minimizing fructose or even simple sugar intake, and then physical activity. And bottom line is for activity, brisk walking might be beneficial. It might be adequate enough for them, so that's definitely a good place to start and, generally, pretty well accepted by our patients.

And then as far as lean NAFLD patients, focusing on the diet modification and increasing physical activity to change their body composition and to improve their metabolic profile seems to be the way to go, since they don't have weight to lose. And vitamin E, the 800 IUs per day could be considered in non-diabetics with biopsy-proven NASH. And then we're looking forward to more research on potential benefits of coffee and tea intake, moderate alcohol consumption as well as omega 3 fatty acids. And that's all.