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Unveiling the Dual Nature of Fatty Liver Disease

Analysis by Dr. Joseph Mercola | January 02, 2025

STORY AT-A-GLANCE

- Nonalcoholic fatty liver disease (NAFLD), now known as metabolic-associated fatty liver disease (MASLD), occurs when excess fat accumulates in the liver, leading to inflammation, scarring and liver failure, with prevalence increasing significantly among older adults
- MASLD has two distinct forms — liver-specific, which is more aggressive and confined to the liver, and systemic, which affects other organs and increases cardiometabolic risk
- Genetic factors, including 27 identified loci, influence MASLD by disrupting fat metabolism in liver cells, contributing to inflammation, triglyceride buildup and liver damage
- Lifestyle contributors to MASLD include insulin resistance, poor diet, physical inactivity and certain medications, all of which promote fat storage and impair liver function
- Lifestyle interventions help address MASLD at its root; these include eliminating harmful fats, optimizing nutrient intake, maintaining a healthy weight and taking liver-supporting supplements

Nonalcoholic fatty liver disease (NAFLD) occurs when excess fat accumulates in your liver without heavy alcohol use. In the United States, NAFLD is particularly prevalent among older adults. Initially, you might not notice any symptoms, but as NAFLD progresses, it will lead to liver inflammation, scarring and even liver failure. If left untreated, NAFLD can advance to more severe liver conditions such as nonalcoholic steatohepatitis (NASH), cirrhosis and liver cancer.

A study published in BMC Gastroenterology[1] found that 40.3% of individuals aged 60 to 74 and 39.2% of those over 74 have NAFLD. For those between 60 and 74 years old, NAFLD is linked to a 60% higher risk of all-cause mortality within five years and a 22% higher risk within 10 years.

Cardiovascular mortality also more than doubles in this age group over a five-year period. However, these increased risks are not observed in those older than 74, indicating that the disease's impact could lessen with advanced age.

In 2023, the term NAFLD was replaced with MASLD (metabolic dysfunction-associated steatotic liver disease) to more accurately highlight its root cause — metabolic dysfunction.[2] Ongoing research continues to expand our understanding of this condition, now revealing two distinct forms — one that is liver-specific and another with systemic effects.

From NAFLD to MASLD — What's Changed?

While NAFLD was defined by the absence of alcohol-related liver damage, MASLD emphasizes the role of common metabolic factors, such as obesity, Type 2 diabetes and metabolic syndrome, in driving liver fat accumulation and inflammation. MASLD also introduces a more precise diagnostic framework. Unlike NAFLD, which primarily excluded other causes of liver disease, MASLD requires evidence of metabolic dysfunction alongside liver fat accumulation.[3]

MASLD develops from a combination of genetic, metabolic and lifestyle factors. Genetic predisposition significantly influences how your body processes fats and sugars, while insulin resistance, a hallmark of metabolic syndrome, exacerbates this process by impairing the liver's ability to manage glucose and fats and promoting fat storage.

As the liver becomes overloaded with fat, inflammation is triggered, leading to liver cell damage. Contributing factors also include poor diet, lack of physical activity and certain medications that increase liver fat accumulation. Diagnosing MASLD presents unique challenges, especially in its early stages when symptoms are subtle or absent.

While liver biopsies remain the gold standard for diagnosis, their invasive nature limits widespread use. Noninvasive tests, like imaging and blood tests, help identify liver fat but often fall short in distinguishing between simple steatosis and more severe forms like NASH. The lack of precise biomarkers and the overlap of symptoms with other liver diseases further complicates diagnosis.

New Insights Into MASLD Reveal Distinct Disease Types

A recent study published in Nature Medicine[4] uncovered the genetic foundations of MASLD and differentiated its various forms. By analyzing genetic data from a large cohort of 36,394 individuals and validating the findings in four additional groups of 3,903 participants, researchers identified genetic markers that provide insights into why MASLD manifests differently among individuals.

One of the most significant findings was the identification of 27 new genetic loci linked to MASLD. These specific locations on the genome influence the development and progression of the disease by impacting how liver cells process and store fats. Using polygenic risk scores, which aggregate the effects of multiple genetic variants, the researchers identified two distinct types of MASLD.

The first type is confined to the liver, leading to more aggressive liver disease. The second is systemic, meaning it impacts multiple organs and significantly raises the risk of cardiometabolic problems, including heart failure. This distinction is important because it implies that treatment and management strategies need to be tailored to the specific type of MASLD a patient has, rather than treating the condition as a single disease.

Another key insight is the strong connection between body fat distribution and liver health. Visceral fat, which is stored around the organs, was found to be the strongest predictor of liver triglyceride content and inflammation. Other measures like body mass index (BMI) and waist-to-hip ratio, which are indicators of overall fat distribution, were also linked to liver health, though they were less impactful than visceral fat in predicting liver damage.[5]

At a genetic level, the researchers found that certain gene variants increase liver fat by disrupting how liver cells handle and secrete lipids. Specifically, some genes that impair the secretion of very low-density lipoproteins (VLDL) cause triglycerides to build up in the liver, increasing the risk of liver-related conditions.

Paradoxically, this retention of triglycerides lowers the levels of circulating lipoproteins in the blood, which appears to reduce the risk of cardiovascular disease (CVD), such as hypertension or heart failure. This suggests that the relationship between MASLD and heart disease is more complex than previously thought.[6]

The study[7] also revealed that the discordant polygenic risk score, which focuses on liver-specific genetic variants like PNPLA3 and TM6SF2, explained a larger portion of the genetic variability in MASLD compared to the concordant score, which reflects genes affecting both liver and systemic health. This highlights the role of liver-specific genetic factors in the development of MASLD.

Both risk scores were also associated with an increased risk of MASLD and severe complications like hepatocellular carcinoma, a type of liver cancer, though the association was stronger for the discordant score. Interestingly, the discordant polygenic risk score was linked to a decreased risk of CVD, whereas the concordant score showed a strong association with a higher risk of CVD and heart failure.

Understanding these pathways is essential for developing targeted therapies, ultimately improving outcomes and reducing the burden of this complex condition. For instance, treatments that enhance VLDL secretion mitigate liver-specific MASLD without impacting cardiovascular risk. On the other hand, interventions aimed at regulating systemic lipid metabolism address the broader cardiometabolic risks associated with the other form of MASLD.[8]

Distinguishing Between Simple Steatosis and NASH

A study published in Current Hepatology Reports[9] provides important context for the progression of MASLD. The researchers examined two major subtypes of what was then

classified as NAFLD — simple steatosis and nonalcoholic steatohepatitis (NASH), now known as metabolic dysfunction-associated steatohepatitis (MASH).

Although this study predates the reclassification, it laid important groundwork by determining the differences between these two conditions in terms of pathophysiology, management and long-term outcomes.

The researchers found that simple steatosis, defined as fat buildup in the liver without inflammation or scarring, is largely benign and does not significantly impact survival. Most individuals with steatosis maintain a normal lifespan, as the excess fat alone doesn't cause liver damage.

In contrast, NASH is a more severe condition that involves inflammation and scarring of the liver (fibrosis), increasing the risk of cirrhosis, liver failure and liver cancer. NASH has become one of the leading causes of liver transplants in the U.S., whereas simple steatosis rarely requires such drastic interventions. The study also found a strong link between NASH and metabolic syndrome, noting that individuals with obesity, Type 2 diabetes or high triglycerides are at a higher risk.

Distinguishing between simple steatosis and NASH is essential for effective management and improving long-term outcomes. "As the prevalence of NAFLD continues to increase, further research is needed to develop noninvasive diagnostic approaches and management algorithms," the researchers concluded.[10]

Helpful Strategies to Address MASLD at Its Root

Adopting healthy lifestyle and dietary habits to address the root causes of metabolic dysfunction not only supports optimal liver function and reduces your risk of MASLD, but also promotes long-term health and vitality. Here are some key strategies I recommend:

1. **Eliminate harmful fats from your diet —** Remove all vegetable oils, including canola, soybean, corn and sunflower oils, from your diet, as they disrupt mitochondrial function and promote inflammation. Instead, use healthier fats like grass fed tallow,

ghee or butter. Minimize even "healthy" oils like olive oil, as their monounsaturated fat content also impairs metabolic function when consumed excessively.

2. **Optimize your carbohydrate intake —** Aim for a minimum of 200 to 250 grams of targeted carbohydrates daily, adjusting upwards if you are highly active, based on your microbiome. Begin with fruit juice containing pulp and whole fruit, as these support gut healing with fiber and natural sugars.

   Transition to pulp-free juice only after your digestion has improved, sipping it slowly to avoid metabolic stress, similar to dextrose water for severely compromised gut health. As your digestion strengthens, introduce complex carbohydrates and starches gradually to maintain balanced energy and support metabolic function.

3. **Balance your protein sources —** Ensure that one-third of your daily protein intake consists of collagen, targeting approximately 0.8 grams of protein per pound of lean body mass, which should make up about 15% of your total calorie intake. Choose grass fed ruminant meats over conventional chicken or pork to reduce exposure to harmful linoleic acid (LA) and support optimal metabolic health.

4. **Prioritize choline-rich foods —** Choline is important for moving fat out of the liver and lowering the risk of fatty liver disease. Increase your intake of foods like organic, pasture-raised egg yolks, grass fed beef liver and arugula to increase your intake of this nutrient.

5. **Focus on eating whole, nutrient-dense foods —** Eliminate ultraprocessed foods, including fast foods, from your diet, as they're loaded with refined carbohydrates, vegetable oils, preservatives and other harmful ingredients that overwhelm your liver and contribute to dysfunction. Instead, replace them with whole, minimally processed, nutrient-dense foods to stabilize your blood sugar, reduce inflammation and reduce the burden on your liver.

6. **Maintain a healthy weight —** Regular exercise is essential for boosting metabolism and supporting a healthy weight. If you're overweight, losing 7% to 10% of your body

weight helps improve NAFLD, including lowering liver fat content, liver inflammation and fibrosis.[11]

7. **Consider taking liver-supporting supplements —** Supporting your liver with targeted nutrients not only protects against damage but also enhances its ability to detoxify and regenerate. Vitamin B12 and folate work together to reduce inflammation and prevent fibrosis by keeping homocysteine levels in check.[12]

   To further protect and detoxify the liver, n-acetylcysteine (NAC) boosts glutathione production, a powerful antioxidant that neutralizes toxins and reduces oxidative stress.[13]

   In addition to antioxidants, supplements like milk thistle and CoQ10 offer unique benefits. The active compounds in milk thistle, silymarin and silybin, act as shields against harmful toxins while promoting the repair and regeneration of damaged liver cells.[14] Meanwhile, CoQ10 plays a role in supporting mitochondrial health, ensuring your liver has the energy it needs to function efficiently while reducing inflammation and oxidative damage.[15]

   Magnesium is another important nutrient for liver health, particularly in its role in cellular energy production. To determine your ideal dosage, take magnesium citrate first, gradually increasing your dose until you experience loose stools, then reduce it slightly — that's your ideal dose. Afterward, transition to magnesium threonate, which doesn't cause loose stools like magnesium citrate.

Sources and References

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