

# METABOLIC SYNDROME INSIGHTS & OUTCOMES

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## Obesity and Nonalcoholic Fatty Liver Disease

Add nonalcoholic fatty liver disease (NAFLD) to the list of emerging health problems associated with the current epidemic of obesity—and to the list of conditions that health care providers are likely to encounter in patients with metabolic syndrome or diabetes. NAFLD encompasses a group of liver disorders that, although unrelated to alcohol consumption, manifest a similar macrovesicular hepatic steatosis.

NAFLD affects 10 to 24 percent of the general population, nearly 5 percent of children, and 57 to 74 percent of obese people. While simple fatty liver usually isn't a serious concern, 2 to 5 percent of American adults and up to 20 percent of obese individuals develop nonalcoholic steatohepatitis (NASH). Characterized by histologic inflammation and fibrosis, this serious form of NAFLD leads to cirrhosis in about one in 30 patients and significantly increases the risk for hepatocellular carcinoma.

### NAFLD PRECURSORS

Many patients with NASH have elevated cholesterol and triglycerides and are overweight or obese. More than 40 percent of people with NAFLD have metabolic syndrome. The liver injury of NASH is thought to be due to insulin resistance, disturbances of glucose and lipid metabolism, and release of inflammatory cytokines. Free fatty acids released from visceral fat accumulate in hepatocytes, where they disrupt fatty acid oxidation and lead to free radical formation.

### WHEN TO TAKE NOTICE

According to the American Gastroenterological Association, the following risk factors warrant consideration of underlying NAFLD: obesity, diabetes, hypertriglyceridemia, and elevated serum alanine aminotransferase (ALT) (in the absence of another cause).

Both fatty liver and NASH are asymptomatic in a large fraction of patients. NAFLD is often discovered when the patient undergoes routine biochemical evaluation of another medical condition (it is found on routine blood testing, not by radiologic or other means). A physical exam in children may find a slightly enlarged liver. Mildly to moderately elevated levels of ALT and/or aspartate aminotransferase (AST) are common but not universally present. Some patients may have elevated serum ferritin or transferrin saturation. About one-quarter of NASH patients have elevated serum IgA, one-third of NAFLD patients have hyperglycemia, and

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## Are Diuretics the Best Option for Hypertension in Metabolic Syndrome?

Diuretics may be a better treatment than other antihypertensive agents for patients with hypertension and metabolic syndrome, according to newly released findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

**Better outcomes.** In an analysis of treatment outcomes in more than 23,000 patients with metabolic syndrome who were followed for up to six years, a thiazide diuretic led to better cardiovascular and renal outcomes than an ACE inhibitor, a calcium channel blocker, or an alpha-blocker.

Patients randomized to receive the diuretic had significantly lower rates of heart failure and combined cardiovascular disease. In addition, black patients with metabolic syndrome who received a thiazide diuretic had lower rates of stroke and end-stage renal disease.

**A better choice for initial therapy.** Although ACE inhibitors, calcium channel blockers, and alpha-blockers may have more favorable metabolic profiles, the researchers concluded that their preferred use as initial therapy in hypertensive patients with metabolic syndrome is not supported. Particularly for black patients, thiazide diuretics may be the better choice.

More information can be found at <http://allhat.sph.uth.tmc.edu>.

## TLC: Benefits and Challenges

The comedian Phyllis Diller once said, “My idea of exercise is a good brisk sit.” When treating patients with metabolic syndrome, one hopes they don’t follow in her footsteps. Lifestyle change, including exercise, is the first-line therapy for metabolic syndrome and an essential approach for preventing and treating obesity, dyslipidemia, hypertension, and insulin resistance.

Briefly, Therapeutic Lifestyle Changes (TLC) recommended by the National Heart, Lung, and Blood Institute and the American Heart Association include:

- Weight loss in overweight or obese people
- Increased physical activity
- A prudent diet

### DOES TLC WORK?

Several studies indicate that it does. For example, in a small, four-week, randomized controlled trial of exercise, diet, and other lifestyle modifications, women with metabolic syndrome who received lifestyle intervention experienced significant improvements in weight, waist circumference, triglycerides, HDL cholesterol, LDL cholesterol, systolic blood pressure, and fasting glucose. Larger trials have also shown benefits. In the Diabetes Prevention Program Trial of more than 3,000 patients with impaired glucose tolerance, incidence of metabolic syndrome dropped by 41 percent in patients receiving lifestyle intervention (at least 150 minutes of exercise per week plus diet changes). Among those with metabolic syndrome at baseline, 18 percent of the placebo group, 23 percent of the metformin group, and 38 percent of the lifestyle intervention group no longer had the syndrome at three years.

Goals of TLC include:

- Reducing body weight by 7 to 10 percent in the first year (and eventually achieving a BMI of less than 25) by balancing caloric intake and physical activity
- Getting 30 minutes of moderately intense physical activity at least five days a week
- Limiting saturated fat to less than 7 percent of calories and cholesterol to less than 200 milligrams per day

In addition, consider limiting alcohol, sodium, and sugar and adding 2 grams (g) per day of plant stanols/sterols and 10 to 25 g per day of viscous (soluble) fiber.

### STEPS TO HELP PATIENTS SUCCEED

Helping patients make lasting lifestyle changes is challenging. Most patients don’t achieve their targets because adherence falls off over time. These tactics can help:

- Discuss appropriate lifestyle changes with the patient. Allow him or her to choose one or two changes to focus on initially.
- Provide the patient with appropriate resources and information.
- Refer interested patients to a certified diabetes educator or registered dietitian.
- Follow up frequently to reassess clinical status and modify goals.

Lifestyle changes needn’t be large. Even getting 10 minutes of daily exercise is an improvement over a good brisk sit.





[www.gastro.org](http://www.gastro.org)  
American Gastrointestinal  
Association

[www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)  
National Heart, Lung, and Blood  
Institute

[www.jhucct.com/shhs](http://www.jhucct.com/shhs)  
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# Sleep Disturbances in Patients with Metabolic Syndrome

**Sleep-disordered breathing (SDB) may be more than a local abnormality of the respiratory tract. It may lead to metabolic changes that increase the risk for cardiovascular and cerebrovascular disease.**

Several studies have shown that SDB is more common in patients with metabolic syndrome. While central obesity is a risk factor common to both, there is increasing evidence that sleep disorders independently contribute to cardiovascular and cerebrovascular morbidity.

**Hypertension.** SDB is strongly associated with hypertension. The cyclic intermittent hypoxia caused by upper-airway occlusion triggers sympathetic activation, one mechanism in the development of high blood pressure. Patients with moderate obstructive sleep apnea (OSA) are three times more likely to be hypertensive than patients without OSA. Continuous positive airway pressure (CPAP) therapy in patients with severe (but not mild or moderate) OSA has been shown to lower blood pressure.

**Inflammation and oxidative stress.** Cellular oxidative stress and systemic inflammation are known to raise cardiovascular disease risk. Intermittent hypoxia increases both factors. Several studies have reported higher plasma levels of proinflammatory cytokines in patients with sleep apnea and narcolepsy.

**Insulin resistance and glucose intolerance.** Although studies to date are conflicting, it appears that SDB contributes modestly to insulin resistance via autonomic and neuroendocrine mechanisms and effects on glucose regulation and inflammation. The epidemiologic Sleep Heart Health Study reported an association between OSA and glucose intolerance. Clinical studies have shown that OSA is associated with higher plasma insulin levels and insulin resistance—even in nonobese individuals.

**Dyslipidemia.** Individuals with SDB are more likely to have abnormal lipid profiles, including higher levels of triglycerides and oxidized LDL cholesterol and lower levels of HDL cholesterol. This may be partly due to

greater lipid biosynthesis and peroxidation induced by intermittent hypoxia.

These various factors appear to interact, creating a vicious cycle that further raises cardiovascular risk. For example, although obesity is a risk factor for SDB, SDB itself may encourage weight gain, although, aside from causing fatigue, the exact mechanisms are unclear. More research in this area is needed, but meanwhile, there are implications for patient care. Patients with SDB can benefit from thorough assessment of cardiovascular risk, and health care providers should be cognizant of the possibility of SDB in those with metabolic syndrome. When SDB is present, weight management, diet, and exercise are recommended to improve insulin sensitivity and the overall metabolic profile.



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one-third of NAFLD patients have anti-nuclear antibody. Imaging (sonography, MRI, or CT scan) is the most sensitive method for detecting simply fatty liver or steatosis, while confirmation and staging of fibrosis require liver biopsy and histology.

### MANAGEMENT APPROACHES

Preventing the progression of fatty liver to cirrhosis and liver failure is the key therapy goal. Exercise, a balanced low-calorie diet, and weight loss are the foundations of therapy for both NAFLD and metabolic syndrome. For patients whose body mass index is higher than 25 kg/m<sup>2</sup>, an initial target should be a loss of 7 to 10 percent of current body weight. Rapid weight loss is not a good idea. Losing more than 3.5 pounds per week has been associated with adverse changes in liver histology and a greater risk for steatohepatitis and liver failure. Be sure that patients are aware that a safe rate of weight loss is 1 to 2 pounds a week. Regular exercise, even if it doesn't lead to weight loss, confers important benefits through its impact on skeletal muscle metabolism and insulin sensitivity.

It's not clear whether pharmacological therapy is effective,



but when lifestyle changes don't improve biochemical markers or histology, potentially useful agents to try include:

- Lipid-lowering medications (fibrates and fish oil)
- Weight-loss agents (sibutramine, orlistat)
- Insulin sensitizers (such as metformin and pioglitazone)

Other agents that may be useful include cyto-protective agents (such as ursodeoxycholic acid), antioxidants (such as vitamin E), and anti-inflammatory agents.

It's worthwhile to review the patient's entire medical regimen for hepatotoxic agents that may contribute to fatty liver disease, including glucocorticoids, statins, calcium channel blockers, valproic acid, synthetic estrogens, and tetracycline.

In both metabolic syndrome and NAFLD, patient responsibility is critical—and difficult to achieve. But at a minimum, providers can help their patients identify achievable lifestyle changes and obtain the education needed to reach those goals.