Semaglutide Reduces Liver Fat in People Living With HIV

The diabetes and weight-loss drug also appears to improve biomarkers of inflammation and immune activation.

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Semaglutide (Ozempic or Wegovy), a widely used diabetes and weight-loss drug, reduced liver fat by 31% and may also decrease inflammation in people with HIV and metabolic dysfunction-associated steatotic liver disease (MASLD), according to study results presented last week at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver.

“What we saw were really great, clinically significant reductions in liver fat even over that short period of time,” Jordan Lake, MD, of the University of Texas in Houston, told reporters at a media briefing.

HIV and Fatty Liver Disease

MASLD, the new name for non-alcoholic fatty liver disease (NAFLD), is responsible for a growing share of advanced liver disease worldwide. Fatty liver disease is associated with obesity, type 2 diabetes and other metabolic abnormalities. Over time, the buildup of fat in the liver can lead to inflammation, fibrosis, cirrhosis and liver cancer.

According to the National Institutes of Health, an estimated 30% to 40% of people living with HIV have fatty liver disease, slightly higher than the percentage among HIV-negative people. Earlier in the epidemic, severe hepatomegaly with steatosis (enlarged fatty liver) was a side effect of first-generation nucleoside/nucleotide reverse transcriptase inhibitors, and drugs in that class still carry a warning. Today, other risk factors are more relevant, but HIV likely plays a role in accelerating liver injury, Lake said.

At CROI, Jennifer Price, MD, PhD, of the University of California San Francisco, reported that among 654 people with well-controlled HIV, a high CD4 count and no other known causes of chronic liver disease, 53% showed evidence of MASLD according to transient elastography imaging, and about 20% had moderate to advanced liver fibrosis.

Risk factors for MASLD included older age, male sex, a high body mass index (BMI) or large waist

circumference and high triglycerides, while Black people had lower odds. Liver biopsies showed that, compared with HIV-negative people, those with HIV were less likely to have liver steatosis, inflammation or "ballooning" of liver cells, but more likely to have fibrosis. "These findings may suggest that HIV-specific factors beyond necroinflammation contribute to hepatic fibrosis" in HIV-positive people with MASLD, the researchers concluded.

Semaglutide and MASLD

There are currently no approved medical therapies for fatty liver disease, and management has relied on lifestyle changes such as weight loss and exercise. Researchers have studied a wide variety of potential therapies for MASLD and its more severe form, metabolic dysfunction-associated steatohepatitis (MASH), but numerous medications that looked promising in early studies did not pan out in larger trials.

One possible treatment approach is glucagon-like peptide-1 (GLP-1) agonists, which mimic a natural hormone that suppresses appetite, regulates insulin and blood sugar and slows emptying of the stomach. One of these, semaglutide, is approved for the treatment of type 2 diabetes under the brand name Ozempic and for obesity under the brand name Wegovy. Recent studies have shown that semaglutide reduces the risk of cardiovascular events and kidney disease progression in HIV-negative people.

Semaglutide and other weight-loss medications, including tirzepatide (Mounjaro or Zepbound), appear to work well for people with HIV, although data are limited. Heidi Crane, MD, of the University of Washington in Seattle presented further evidence at CROI, showing that semaglutide led to significant weight loss among people with HIV (an average of about 14 pounds, or about 6% of their body weight) over one year. Those who started with the highest BMI lost the most weight (about 19 pounds), and people without diabetes lost even more weight than those with the condition.

At the same session, Lake presented results from SLIM LIVER (ACTG A5371; NCT04216589), a Phase IIb trial to evaluate the effects of semaglutide on liver fat in people with HIV.

[Update: The SLIM LIVER findings were published online April 30 in the Annals of Internal Medicine.]

Studies of semaglutide for MASH have yielded mixed results, although tirzepatide and the experimental weight-loss drugs retatrutide and survodutide look promising in studies of HIV-negative people. SLIM LIVER evaluated the drug for earlier-stage disease, aiming to improve cardiometabolic health by reducing weight and liver fat. "It's more of a way to either treat or prevent early disease, not a way to reverse existing liver disease," Lake said.

The pilot study, funded by the National Institutes of Health, enrolled 51 adults on suppressive antiretroviral therapy (mostly using integrase inhibitors) with MASLD. They had at least 5% liver fat content according to MRI imaging plus cardiovascular risk factors such as a large waist

circumference, insulin resistance or pre-diabetes. More than half were men, 18 were cisgender women and six were transgender women. The participants were racially/ethnically diverse: 39% Latino, 33% Black, 27% white and 2% Native American. The median BMI was within the range for obesity.

Participants self-administered subcutaneous injections of semaglutide once weekly for 24 weeks, ramping up the dose to 1.0 milligrams. They used the lower dose approved for diabetes because the higher weight-loss dose was not yet available, Lake noted. At six months, the mean absolute decline in liver fat was 4% while the mean relative decline was 31%. More than a quarter (29%) experienced complete MASLD resolution and 58% had at least a 30% relative decline in liver fat (the level associated with histological improvements on a biopsy).

The reduction in liver fat was accompanied by significant improvements in weight (a median 17 pound loss), waist circumference and fasting glucose and triglyceride levels. Women, people over 60, and Latino and white participants experienced more liver fat reduction. Around 20% of participants did not respond to semaglutide, similar to the proportion in the general population.

Semaglutide was generally well tolerated, with just two severe adverse events possibly related to treatment. Side effects were similar to those seen in the general population (mainly gastrointestinal), and there were no additional safety signals specific to people with HIV.

Semaglutide is a safe and effective pharmacologic therapy for MASLD in people with HIV, the researchers concluded. Weight loss and liver fat reduction were “very tightly correlated,” Lake reported. “If you responded and lost weight, then your liver fat got better, and if you did not respond and you did not lose weight, then you also did not have improvements in your liver fat

Overall psoas muscle volume decreased but muscle fat content did not change significantly over the 24 weeks on semaglutide. The volume decrease was greatest among people over age 60, but no sex differences were observed. Participants did not experience a decline in muscle function; in fact, they saw a small improvements in time to do chair rises and walking speed, though these changes did not reach statistical significance, Ditzenberg reported.

The researchers evaluated changes in muscle quality, quantity and function, focusing on the psoas, a pair of large core muscles that run from the lower back through the pelvis to the thigh bone. Psoas volume and fat content were assessed from liver MRIs, and physical function was measured by chair-rise and gait speed tests at baseline and six months.

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Speaking from the audience, Frank Palella, MD, director of the Potocsnak HIV and Aging Center at Northwestern University, suggested that given the benefits of substantial weight loss, some

muscle loss might not matter if function is maintained.

Semaglutide and Inflammation

In her presentation, Lake said that while traditional risk factors are driving fatty liver disease in most people with HIV, "we do think there is a component of liver disease that is HIV-specific, so some of the secondary effects of semaglutide may have unique benefits in people with HIV."

One of those benefits may be reduced inflammation and immune activation. Allison Ross Eckard, MD, of the Medical University of South Carolina, and colleagues looked at the effect of semaglutide on inflammation and immune biomarkers in people with HIV-associated lipohypertrophy, or abdominal fat accumulation.

This analysis included 108 nondiabetic adults on stable antiretroviral therapy with viral suppression. They had a BMI of 25 or higher (indicating overweight or obesity), a large waist circumference or waist-to-hip ratio and reported that they developed increased abdominal girth after starting antiretrovirals. They were randomly assigned to receive semaglutide or placebo injections once weekly for 32 weeks.

At IDWeek 2023, senior investigator Grace McComsey, MD, of Case Western Reserve University, reported that semaglutide significantly decreased central fat in people with lipohypertrophy, primarily driven by a reduction in visceral adipose tissue. McComsey noted that it's not just weight that matters, but also where fat is located. Visceral fat deep within the abdomen is more strongly associated with cardiovascular disease and other health problems.

The new analysis assessed immune activation biomarkers that are known to be increased in people with HIV and are associated with cardiovascular disease. In the semaglutide group, the researchers saw significant changes between baseline and 32 weeks for high-sensitivity C-reactive protein (a 40% decrease), interleukin-6 (a 19% decrease) and soluble CD163, a marker of macrophage activation (a 12% decrease). The anti-inflammatory effect of semaglutide was not fully explained by decreases in weight, according to Eckard.

As weight-loss drugs are shown to have benefits beyond diabetes and obesity, their high cost—which is often not covered by insurance—is a growing concern. While these medications could be cost-saving in the long run, they have the potential to overwhelm Medicaid, Medicare and private insurers. Making these drugs available to all Americans with obesity could cost over $1 trillion per year, according to a New York Times opinion piece. These therapies are even more out of reach for people in low- and middle-income countries. "We should be working with the Medicines Patent Pool so that people in South Africa and other countries with obesity epidemics also have access to this product," HIV advocate Simon Collins urged at the media briefing.

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