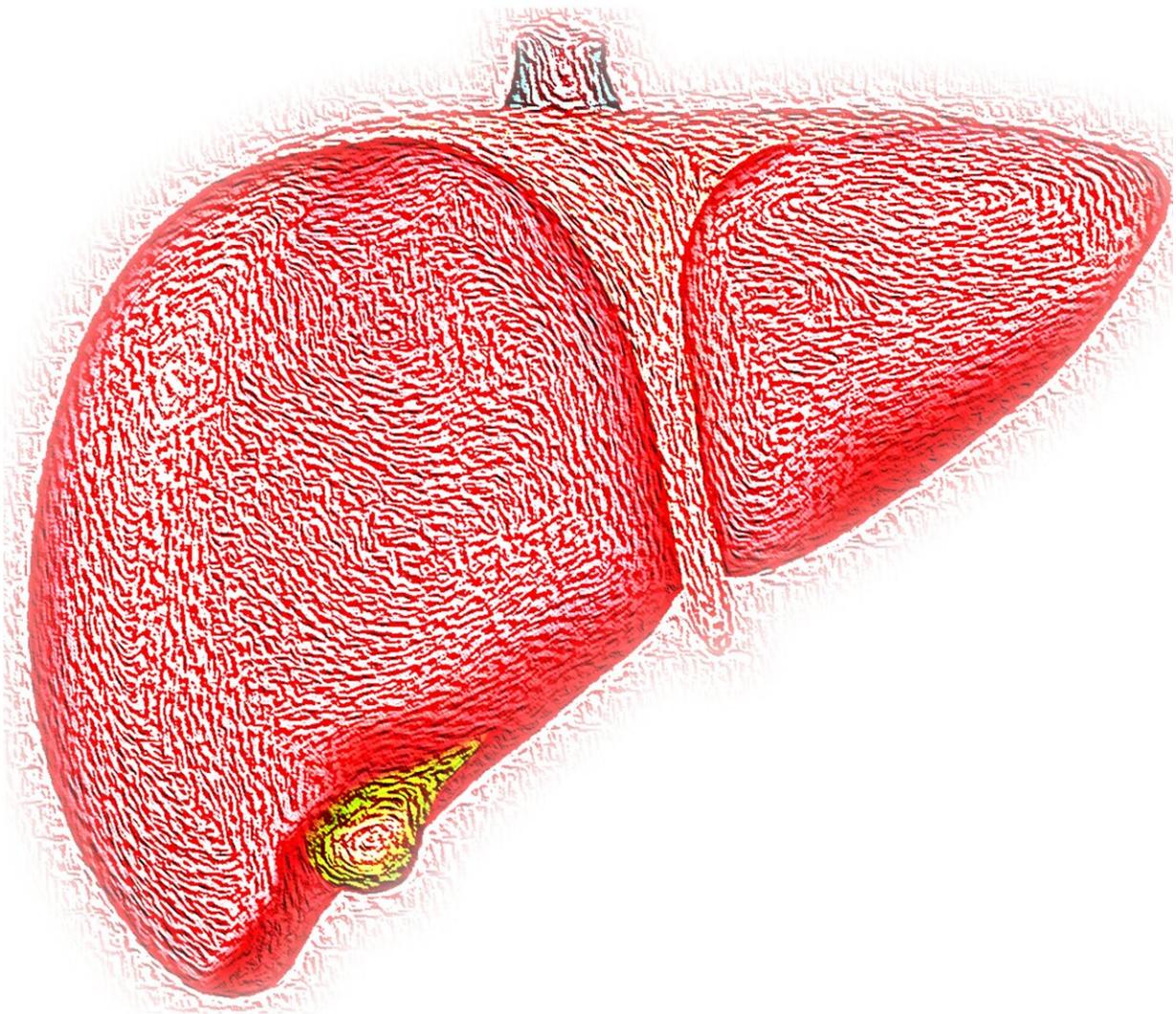


New potential therapy for fatty liver disease

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In those with fatty liver disease, a person's fat goes to their liver instead of their fat tissue, either because of an absence of fat depots, which is seen in the rare genetic disease lipodystrophy, or because the depots are too full, which is seen in people with obesity.

One third of these people will go on to develop nonalcoholic steatohepatitis, or NASH—an advanced form of [fatty liver disease](#) brought on by progressive inflammation and scarring in the organ.

In 2002, Michigan Medicine endocrinologist Elif Oral, M.D., who had just moved from the National Institutes of Health at the time, published her discovery that patients with severe lipodystrophy lack leptin, a hormone that helps curb appetite and control weight gain. When given leptin as a supplement, the patient's serious metabolic abnormalities like NASH improved substantially.

Oral set out to U-M to further study the role of leptin, now in more common forms of NASH. Almost two decades later, her research team found that whether from a leptin deficiency or the presence of partial lipodystrophy, patients with NASH and relatively low leptin levels can mobilize the extra fat in their [liver](#), out of their liver, and help reverse their condition by undergoing leptin therapy.

"Familial partial lipodystrophy often accompanies NASH. It's a rare, genetic condition where patients have a lack of fat in their extremities but remain fat in their [upper body](#)," Oral explained. "I wanted to test the effect of leptin in both those with this rare condition and those that just present with NASH to see if there would be a difference in therapeutic outcomes."

This work, which is the first of its kind in humans and compiles research

from three different studies, showed that leptin is an important signal in regulating fat deposition in the liver, and reversing fat deposition and its subsequent NASH.

During the lifetime of the study, the manufacturer of leptin changed several times, posing substantial bureaucratic obstacles for the research team to overcome.

"I could've moved on to something easier to study, but I wanted to see this through. This is my life's work," Oral said. "I'm grateful for all of my collaborators and co-authors for sticking with me through it all."

As outlined in *Med: Cell Press*, Oral and her team conducted two open-label trials studying nine [male patients](#) with NASH and relatively low leptin levels (less than 9 ng/ml) and 23 patients with both partial lipodystrophy and NASH. Both groups received leptin therapy in the form of metreleptin for one year.

The trials consisted of male patients because Oral found that 35-40% of the men that had leptin levels measured had levels less than the twenty-fifth percentile of their body weight, making them ideal study candidates.

"Not all NASH is created equal. There's a vast distribution of leptin levels in this patient population," Oral said. "High levels of leptin, seen in obesity, can actually be causative of NASH so it was important to carefully select trial participants for low levels."

After blind, paired liver biopsies, both groups were found to have reduced fat in the liver and lower NASH scores after 12 months of leptin therapy. The patients also had improved insulin sensitivity and body weight.

The findings are only applicable to leptin, but Oral thinks other molecules or treatments that activate leptin in the body could be of focus in future studies in an attempt to widen the therapeutic window for these patients.

After obesity is established, there's little gain by giving someone leptin. However, a patient in the early overweight state may get value from undergoing leptin therapy, inspiring the research team to study [leptin](#) as a preventive weight control option in those at risk of crossing the obesity threshold and developing more fat in the liver.

"Although these results were encouraging, this justifies a larger trial," Oral said. "But there's no approved treatments for NASH of any form, so to have a therapeutic that can help at least a fraction of these patients is exciting."

More information: Baris Akinci et al, Metreleptin therapy for nonalcoholic steatohepatitis: Open-label therapy interventions in two different clinical settings, *Med* (2021). [DOI: 10.1016/j.medj.2021.04.001](#)

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