

# Experimental drug reverses high cholesterol, obesity-related nonalcoholic fatty liver disease in animal study

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Scientists have discovered a novel molecular pathway for an enzyme inhibitor in humans that plays a direct role in the development of high cholesterol and nonalcoholic fatty liver disease, which they then were able to reverse in mice with an investigational drug. The study results will be presented Monday at ENDO 2019, the Endocrine Society's annual meeting in New Orleans, La., by researchers from Northwestern University Feinberg School of Medicine in Chicago, Ill.

Northwestern is partnering with Tohoku University in Japan in testing the new oral [drug](#), known as TM5614. It reportedly impedes the action of plasminogen activator inhibitor 1, or PAI-1, a multifunctional protein in the body.

"High blood levels of PAI-1 are a hallmark of obesity, type 2 diabetes and [metabolic syndrome](#), a cluster of risk factors for obesity-related diseases," said the study's lead researcher, Joshua Levine, M.D., Ph.D., an endocrinology fellow at Northwestern. He decided to conduct this study, he said, because a Northwestern research team recently found that people who have a loss-of-function mutation in the gene that codes for PAI-1 have lower fasting insulin levels than unaffected relatives and appear to be protected from developing diabetes. He wondered if blocking PAI-1 could reverse diet-induced obesity and its related health problems.

In this study, the investigators induced obesity in [mice](#) by feeding them, for four months, a high-fat, high-sugar mice chow that Levine said is the equivalent of fast food. The mice then received 10 days of treatment with the PAI-1 inhibitor TM5614.

After a week of treatment, the mice showed significantly improved fasting levels of blood sugar, insulin and LDL, or "bad" cholesterol, compared to untreated mice, the researchers reported. Treated mice also exhibited a "remarkable" reduction in fatty liver disease, Levine said.

Further analysis revealed that PAI-1 prevents the inactivation of PCSK9, a protein that plays a key role in regulating blood cholesterol levels. TM5614 was able to rescue the ability to inactivate PCSK9.

"This is important because PCSK9 inhibitors are the newest drug therapy available for the treatment of high cholesterol for people who do not benefit enough from statin cholesterol-lowering medicines or cannot tolerate statins," Levine said. "However, the high cost of these drugs limits their use, and they are injections, rather than pills."

If the researchers can duplicate the benefits of TM5614 in people, Levine said, "the drug may eventually become a less expensive and easier alternative to PCSK9 inhibitors." He added that there currently is no approved drug therapy for [nonalcoholic fatty liver disease](#).

Provided by The Endocrine Society

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