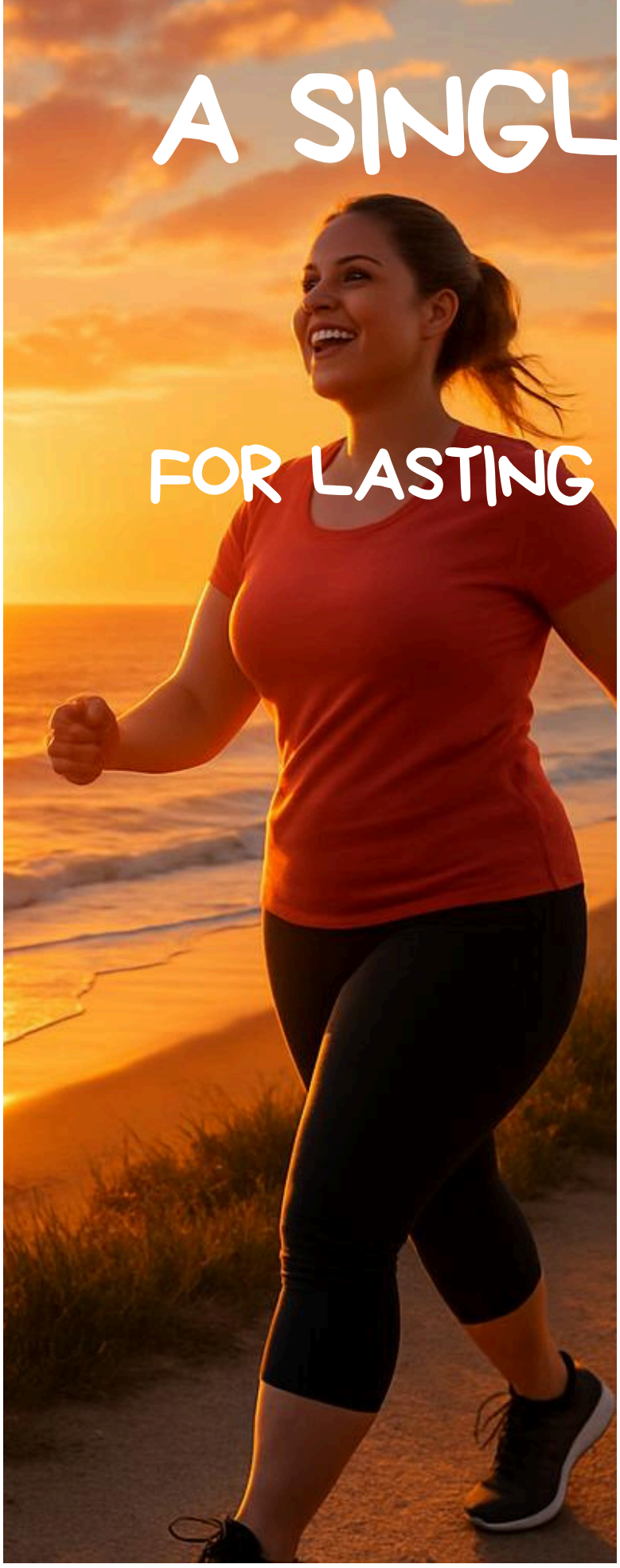


A SINGLE SHOT FOR LASTING WEIGHT-LOSS?

by Cliff Dominy PhD

Scientists have developed a novel genetic therapy that allows the body to produce its own weight-loss hormones, without weekly injections [1].

Researchers from Osaka University in Japan have introduced a gene for a glucagon-like peptide-1 (GLP-1) receptor agonist into the liver of obese mice. The study, reported in July 2025 in Nature Communications Medicine, showed that the gene, once integrated into the liver, reliably produced the foreign GLP-1 hormone - a key player in mammalian weight-loss. The animals that received the gene therapy lost significant weight relative to untreated mice, whilst maintaining normal blood glucose and insulin levels in their bodies.

Currently, the most successful GLP-1 receptor agonists, like Ozempic® and Zepbound®, are injectable formulations. Principal investigator of the study Dr Keiichiro Suzuki noted, "These medications do not stay in the body long, meaning they typically have to be injected weekly, or even daily, to maintain consistent therapeutic levels of the drug." Suzuki's new therapy aimed to provide a lifelong GLP-1 reservoir within the body - a one and done treatment.

A new idea

The proof-of-concept study, termed in vivo targeted integration, proves that whole gene therapy might be possible for the effective management of chronic diseases like obesity and type 2 diabetes. Until now, gene therapy has had success treating diseases caused by mutations in single genes, such as hemophilia B and spinal muscular atrophy. The Osaka group has adapted this approach to treat a far wider range of human disease.

How does it work?

Scientists in the Suzuki laboratory created a hybrid gene containing exendin-4, a first-generation GLP-1 receptor agonist, fused to a signal peptide to ensure its efficient export from the liver. Exendin-4, originally isolated from the saliva of a Gila Monster, was first approved in 2005 by the FDA for the treatment of type 2 diabetes.

Whilst later generations of GLP-1s have improved stability and efficacy, exendin-4 was considered a better choice for the study. The reason being that investigators wanted to minimize the over-accumulation of the drug once it was in continuous production by its new host.

The exendin-4 gene was modified with a liver-associated secretion signal to promote the eventual export of the active hormone into the blood. The DNA was packaged inside a nanoparticle and injected into DIO (diet-induced obese) mice, which had been pre-fattened on a high-fat/ high-sugar diet - the nutritional equivalent of doughnuts.

Benefits that last

The weight-loss experiment ran for 28-weeks, a quarter of a typical mouse's lifespan. The foreign DNA was observed to stably integrate into mouse liver cells and reliably produced and secreted exendin-4 into the bloodstream. Compared to control mice on the same diet, the exendin-4 group showed increased appetite control, consumed fewer calories and lost as much as 30% of their body weight. Furthermore, the animals glucose tolerance and insulin sensitivity were improved. "The results were very exciting," explains Suzuki. "We found that these genome-edited mice produced high levels of Exenatide that could be detected in blood for several months after introduction of the gene." Exenatide is the generic drug name for the exendin-4 peptide hormone.

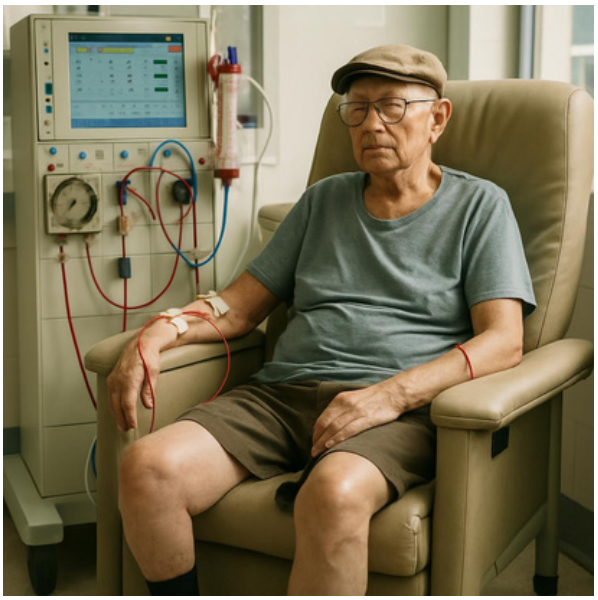
Safety concerns

Off-target effects of any gene therapy are always a concern. These are the unanticipated interactions of the new gene elsewhere in the body. To investigate any potential adverse reactions of the therapy, the group confirmed that there were no signs of exendin-4 integration elsewhere in the mice. The liver itself appeared healthy, despite the introduction of the new gene into its genetic makeup. There was no sign of organ damage, and the animals' markers of liver health were normal.

The long way forward

Chronic diseases like obesity and type 2 diabetes have traditionally not been suited to conventional gene therapies. However, by integrating a gene for a well-described therapeutic hormone into liver cells, the Japanese researchers have created a continuous drug factory within the patient. "We hope that our design of a onetime genetic treatment can be applied to many conditions that do not have exact genetic causes," says Suzuki. Other notable benefits include the patient-centred convenience of the approach and the long-term economic benefits of a one-off treatment option.

The results are promising, but much work needs to be done. An important first step would be to improve the integration efficiency of the gene into the liver - in the paper, just 1% of cells took up the gene. The host immune system's tolerance of the new therapy will need to be fully understood in other species before human trials can begin.



Regulators will almost certainly want to see the inclusion of an "Off-Switch". Lifelong continuous production of a foreign protein by genetically modified liver cells may well carry unforeseeable long-term health consequences. A reliable means of shutting the system down, on demand, would be essential.

Research, as they say, is ongoing.

Reference

Hirose, J., Aizawa, E., Yamamoto, S. et al. Targeted in vivo gene integration of a secretion-enabled GLP-1 receptor agonist reverses diet-induced non-genetic obesity and pre-diabetes. Commun Med 5, 269, 1-11 (2025).