Exercise attenuates semaglutide-induced muscle loss, and in combination reduces MASH and atherosclerosis in obese LDLR-/-.Leiden mice

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1. Background & aims

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is an antidiabetic and obesity medication that has recently been approved for treatment of metabolic dysfunction-associated steatohepatitis (MASH) as well. While the benefits of semaglutide for weight management are encouraging, concomitant muscle loss remains a concern.

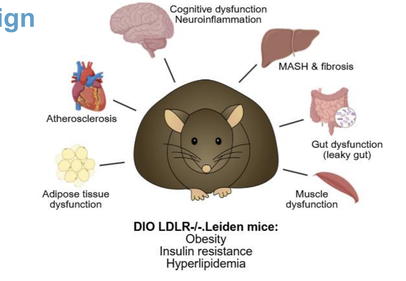
Here, we evaluated the metabolic effects of semaglutide, exercise and the combination thereof in a translational model of diet-induced obesity with a humanized lipid metabolism to explore associated multi-organ complications.

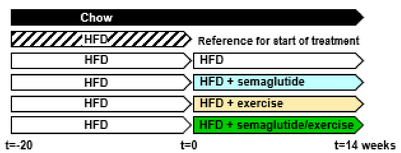
2. Methods & study design

Ldlr-/-.Leiden mice are a model for metabolic dysregulation with development of several comorbidities when fed a high fat diet (HFD).

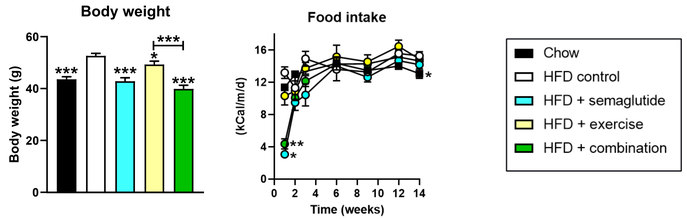
In the current experiment mice were fed the HFD for 20 weeks and were subsequently left untreated (control) or were treated for 14 weeks with semaglutide, exercise (running-wheel) or the combination thereof.

(n=8 chow mice; n=15 HFD mice/group)

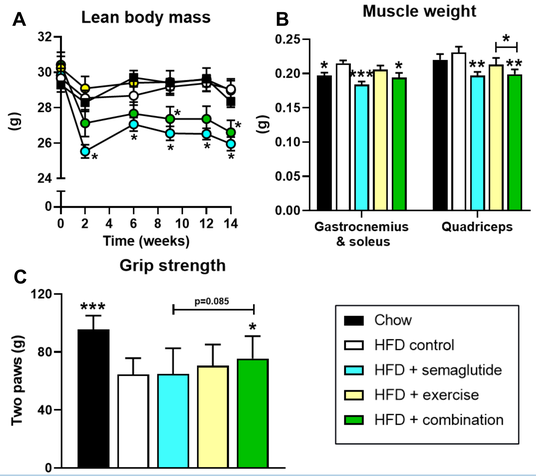




3. Semaglutide decreased body weight and transiently decreased food intake



4. Semaglutide, either alone or in combination with exercise, decreased lean body mass and muscle weights

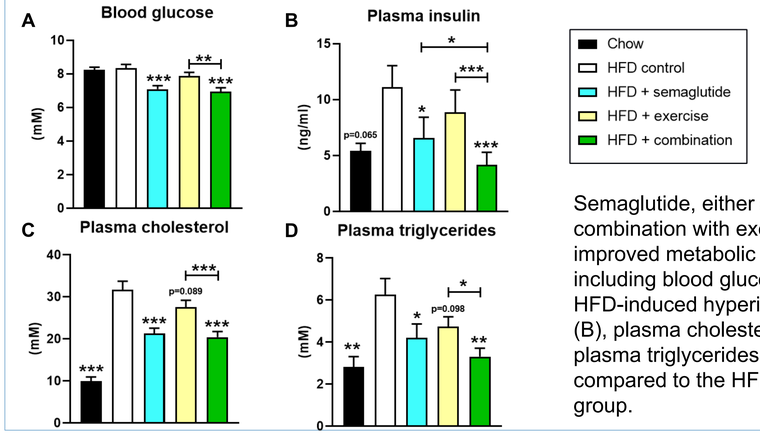


A. Lean body mass was decreased with semaglutide treatment and as well, but to a lesser extent, when combined with exercise.

B. Muscle weights at sacrifice were significantly decreased as compared to HFD control group with semaglutide treatment, but also when combined with exercise.

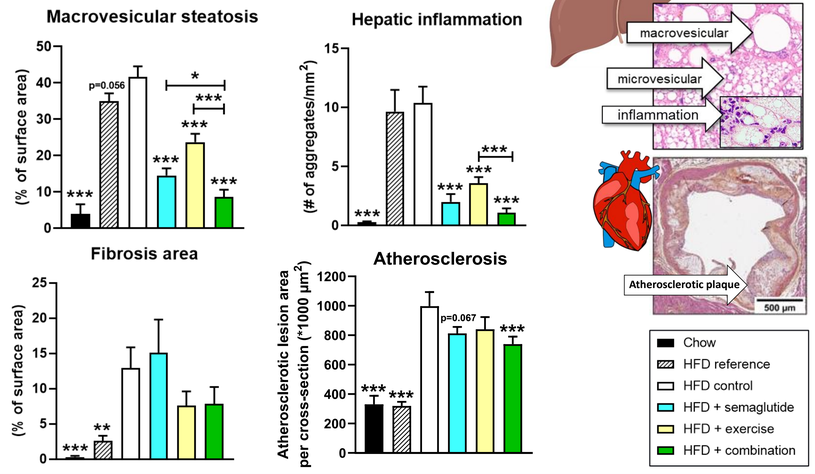
C. Absolute grip strength was improved as compared to HFD control group in combination treatment group only.

5. Semaglutide, either alone or in combination with exercise, improved metabolic parameters



Semaglutide, either alone or in combination with exercise, improved metabolic risk factors including blood glucose (A), and HFD-induced hyperinsulinemia (B), plasma cholesterol (C) and plasma triglycerides (D) as compared to the HFD control group.

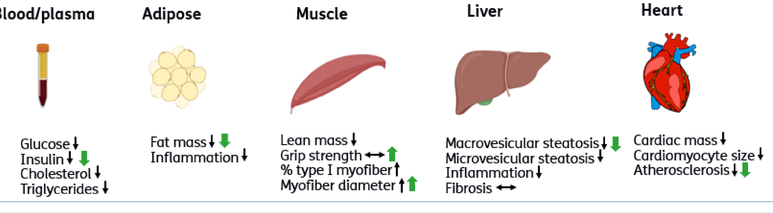
6. All interventions reduced liver steatosis and inflammation, the combination attenuated atherosclerosis



7. Conclusion

Using a translational model of diet-induced obesity with a humanized lipid metabolism, we demonstrated that:

- Semaglutide has broad beneficial effects on metabolic risk factors, adipose tissue inflammation, MASH and cardiac parameters.
- Semaglutide alone also decreases lean body mass and muscle mass.
- **Adding exercise** to the semaglutide intervention attenuated muscle loss and further improved plasma insulin, fat mass reductions, muscle strength, liver steatosis and inflammation, and even attenuated atherosclerosis development.



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