Semaglutide has beneficial effects on non-alcoholic steatohepatitis in Ldlr-/-.Leiden mice

José A. Inia[1,2,3], Geurt Stokman[1], Elsbet J. Pieterman[1], Martine C. Morrison[1], Nicole Worms[1], Lars Verschuren[4], Martien P.M. Caspers[4], Aswin L. Menke[1], Mathieu Petitjean[5], Louis Petitjean[5], Li Chen[5], J. Wouter Jukema[2,3], Hans M.G. Princen[1], Anita M. van den Hoek[1]

[1] Metabolic Health Research, TNO Leiden, The Netherlands, [2] Department of Cardiology and [3] Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Centre, Leiden, The Netherlands, [4] Microbiology and Systems Biology, TNO Zeist, The Netherlands, [5] PharmaNest, Princeton, NJ, USA

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Introduction

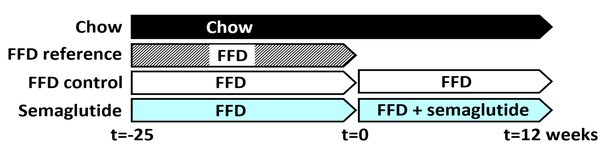
Semaglutide is an agonist of the glucagon-like peptide-1 (GLP-1) receptor that has been approved for the treatment of type II diabetes mellitus and more recently for obesity. Due to their beneficial effects on the metabolic syndrome, GLP-1 receptor agonists are postulated to be promising candidates for the treatment of non-alcoholic steatohepatitis (NASH), the hepatic manifestation of the metabolic syndrome.

Aim

To evaluate the effects of semaglutide in a model with advanced NASH and fibrosis (F3) to investigate its therapeutic potential as NASH agent.

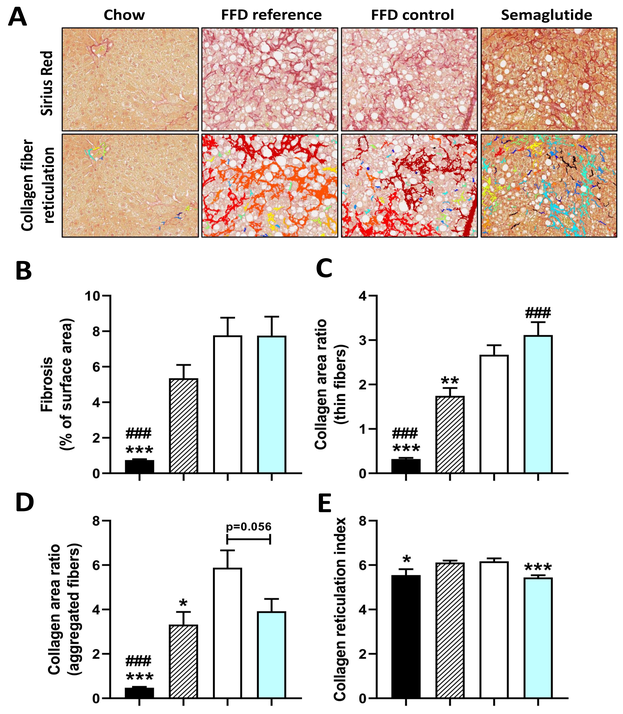
Study design

After 25 weeks on fast food diet (FFD), Ldlr-/-.Leiden mice were treated with 0.12 mg/kg/day semaglutide for twelve weeks on top of the FFD and then compared to the FFD reference or FFD control group. Chow-fed animals were included as healthy reference.



*p<0.05, **p<0.01, ***p<0.001 vs. FFD control, #p<0.05, ##p<0.01, ###p<0.001 vs. FFD reference

Semaglutide does not affect fibrosis quantitatively yet does improve collagen network complexity



Fibrosis levels were unchanged in semaglutide-treated Ldlr-/-.Leiden mice (A, upper panels + B).

However, more refined analysis revealed that semaglutide significantly improved area ratio of thin (C) and aggregated (D) fibers.

Schematic representations of collagen fibers and their intersection points were made (A, lower panels) and quantified. Based on these data the collagen reticulation index was calculated, a measure for fibrosis complexity that was significantly lowered with semaglutide.

Ldlr-/-.Leiden mice on FFD closely represent human NASH and semaglutide improves hepatic fibrosis gene expression

We compared the transcriptome profile of Ldlr-/-.Leiden mice on FFD with a human gene set that differentiated human NASH patients with severe fibrosis from NASH patients with mild fibrosis[1].

In the Ldlr-/-.Leiden mice on FFD, this gene set was upregulated as well (top 15 shown here). Semaglutide predominantly reversed this gene expression that was induced by the FFD.

FFD control *vs.* chow	Semaglutide *vs.* FFD control	
2.96	-1.37	COL1A1
2.84	-0.69	ITGBL1
2.75	-0.35	EPCAM
2.64	-0.35	BICC1
2.63	-0.23	PLCXD3
2.62	-0.35	DPT
2.59	-0.61	SOX4

(continued)

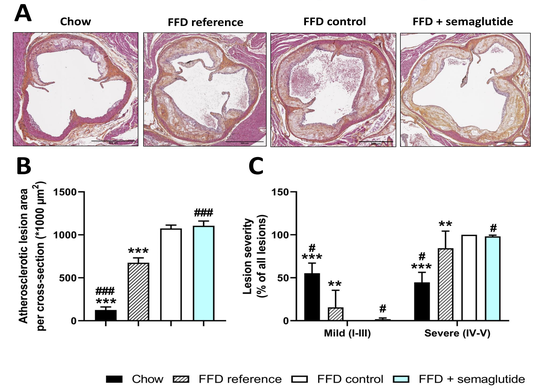
2.54	-0.33	LUM
2.54	-1.04	COL1A2
2.49	-1.17	COL3A1
2.46	-0.33	EHF
2.43	-1.24	VCAN
2.30	-0.55	COL6A3
2.28	-0.34	THBS2
2.24	-0.20	SRPX

[1] Moylan, Hepatology. 2014;59(2):471-482.

Severe atherosclerosis is not counteracted by semaglutide

FFD feeding for 25 weeks induced severe atherosclerosis (A), that was aggravated by an additional 12 weeks on the diet.

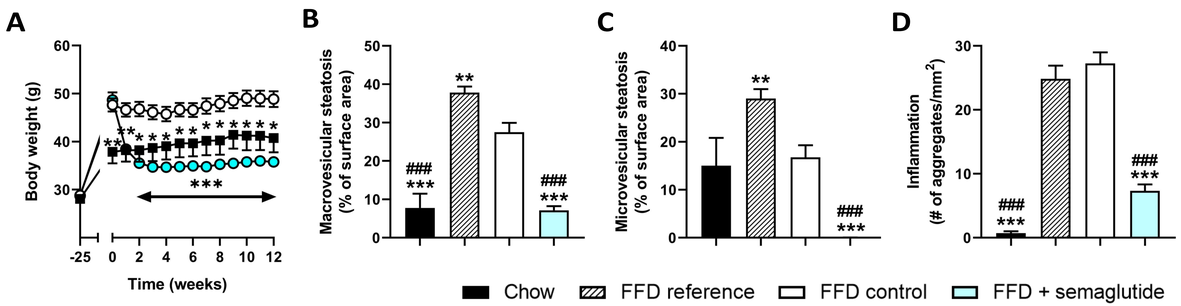
Semaglutide did not hamper the progression of atherosclerosis and both lesion area (B) and lesion severity (C) were comparable to the FFD control group.



Semaglutide strongly improves body weight, hepatic steatosis and hepatic inflammation

Ldlr-/-.Leiden mice developed pronounced obesity compared to mice on the healthy chow diet, though semaglutide treatment resulted in significant reductions in body weight (A).

FFD feeding induced severe hepatic steatosis and inflammation. Semaglutide intervention significantly reduced macrovesicular steatosis (B), microvesicular steatosis (C) and hepatic inflammation (D).



Conclusions

We used a translational model with advanced NASH to demonstrate that semaglutide is a promising candidate with particular potential for the treatment of hepatic steatosis and inflammation, while for reversal of more advanced fibrosis, probably combinations with other NASH agents will be necessary.

Contact information: jose.inia@tno.nl

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