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Therapeutic Potential of DA-1726, a Novel Oxyntomodulin Analogue, in a Diet-Induced NASH Mouse Model

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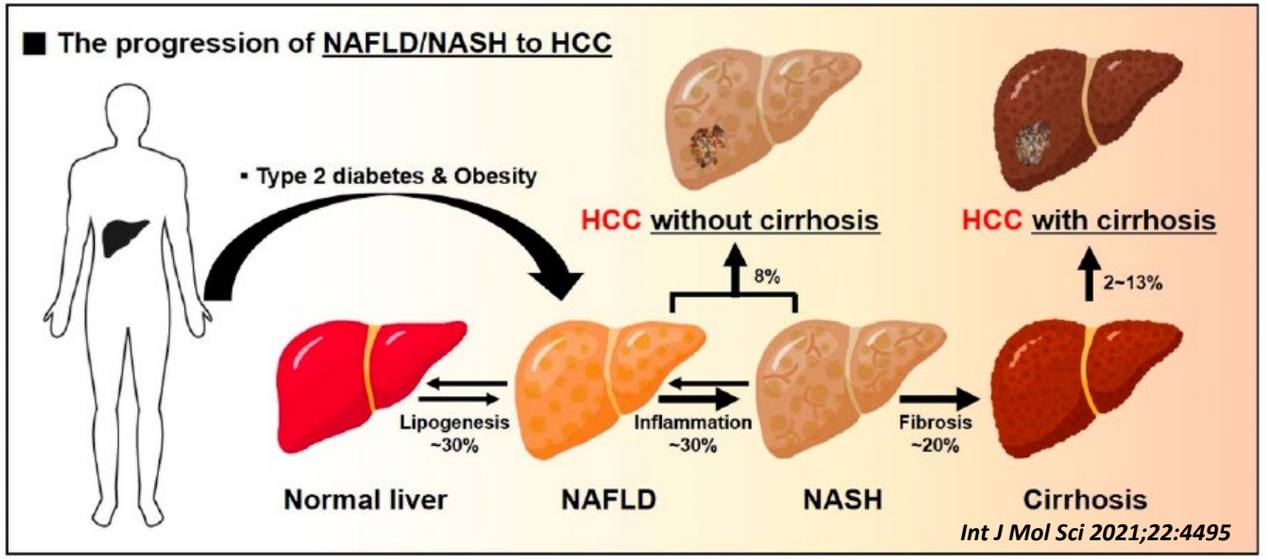
Sunday Jun 5, 2022 12:00 PM - 1:00 PM

American Diabetes Association's 82nd Scientific Sessions, June 3-7, 2022 in New Orleans, Louisiana

DONG-A ST

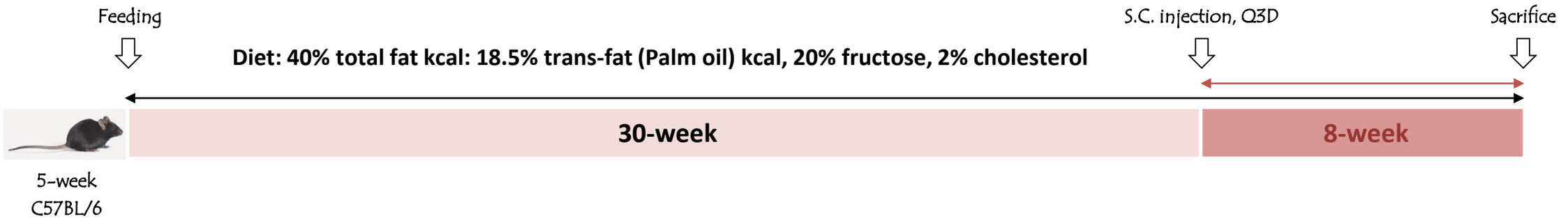
BACKGROUND



- Nonalcoholic fatty liver disease (NAFLD) refers to a spectrum of liver damage that includes a wide range of liver diseases, from steatosis to cirrhosis.
- NAFLD is one of the most common diseases accompanying obesity and type 2 diabetes, and obesity and type 2 diabetes are known to exacerbate the progression of NAFLD to HCC.
- Although there is still no therapeutic agent on the market, clinical results of treatment improvement by GLP-1 and oxyntomodulin analogues have been reported and are in the spotlight.
- Herein, we evaluated the therapeutic potential of DA-1726, a novel oxyntomodulin analogue, for the treatment of non-alcoholic steatohepatitis (NASH).

METHODS

◆ Experiment Scheme

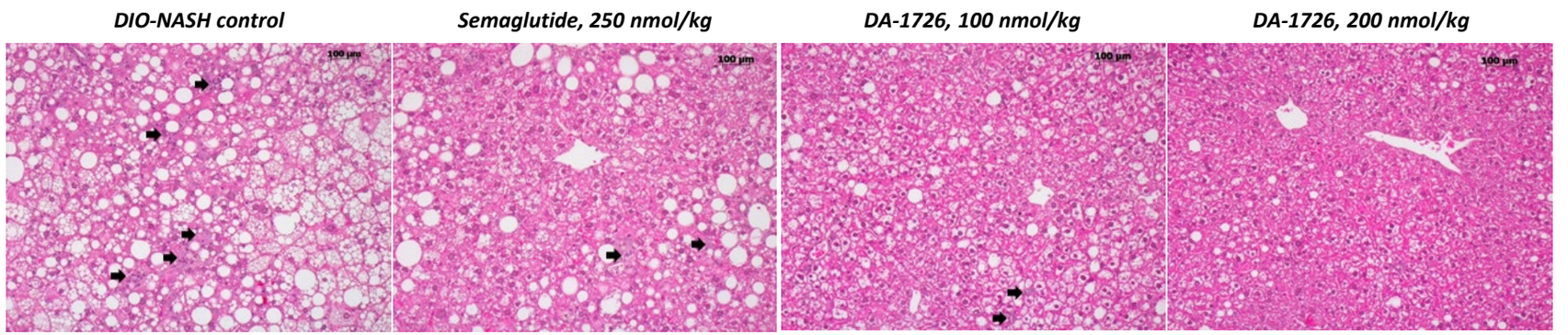


Anti-NASH Effects in DIO-NASH Mice

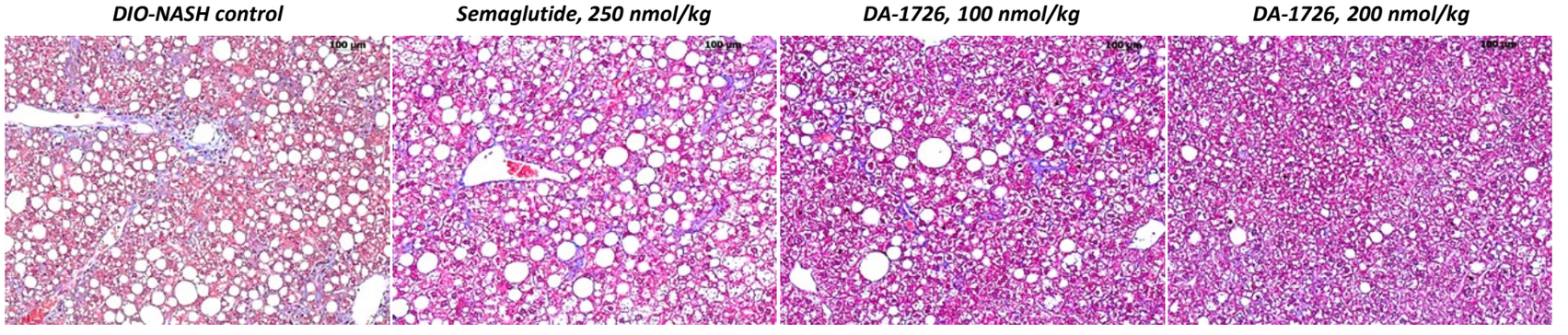
- To induce NASH, male mice were given a diet containing 40% total fat, 20% fructose, and 2% cholesterol for 30 weeks. After then DA-1726 and Semaglutide were subcutaneously injected every three days for 8 weeks. Food consumption and body weight were recorded every three days. At the end of treatment, plasma clinical chemistry parameters (ALT, AST, ALP and T-BIL) and hepatic fat accumulation were detected. And the gene expression of inflammation or fibrosis related markers was analyzed using quantitative RT-PCR in liver tissue.

RESULTS – 1. Histopathological Analysis

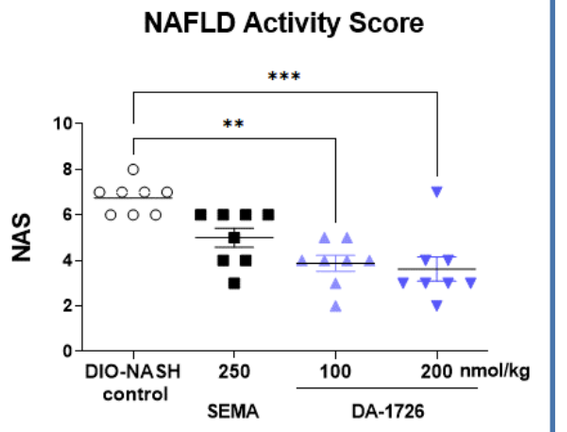
- **DA-1726 further improved hepatic steatosis, inflammation, and fibrosis compared to semaglutide**

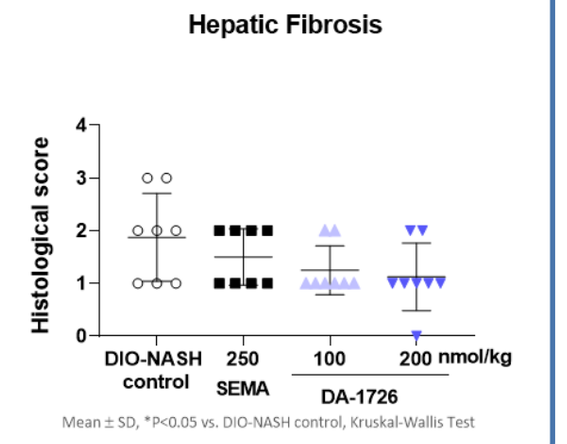


Magnification: × 200; Arrow: Inflammation



Magnification: × 200; Blue color: fibrosis

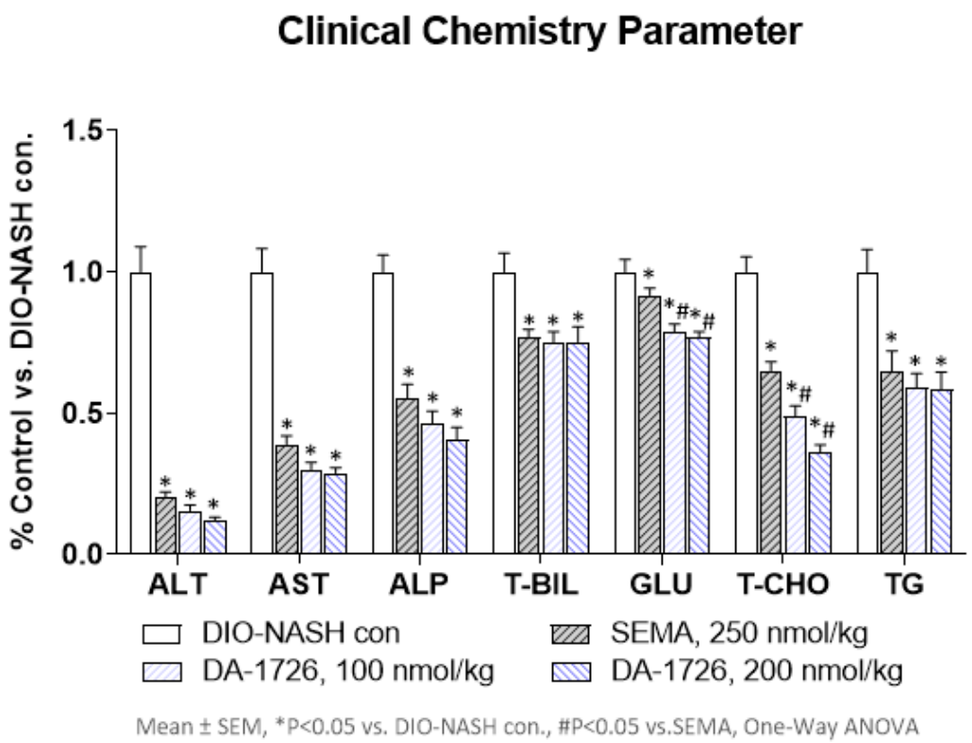


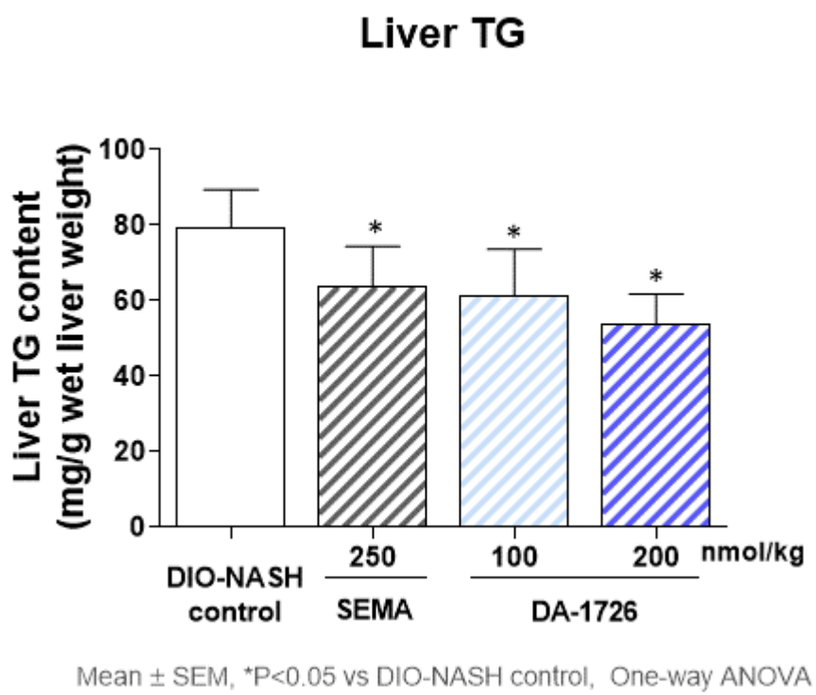


- Abbreviation: SEMA, Semaglutide

RESULTS – 2. Plasma Clinical Chemistry Parameters

- **DA-1726 significantly decreased the plasma clinical chemistry parameters and reduced hepatic TG accumulation**

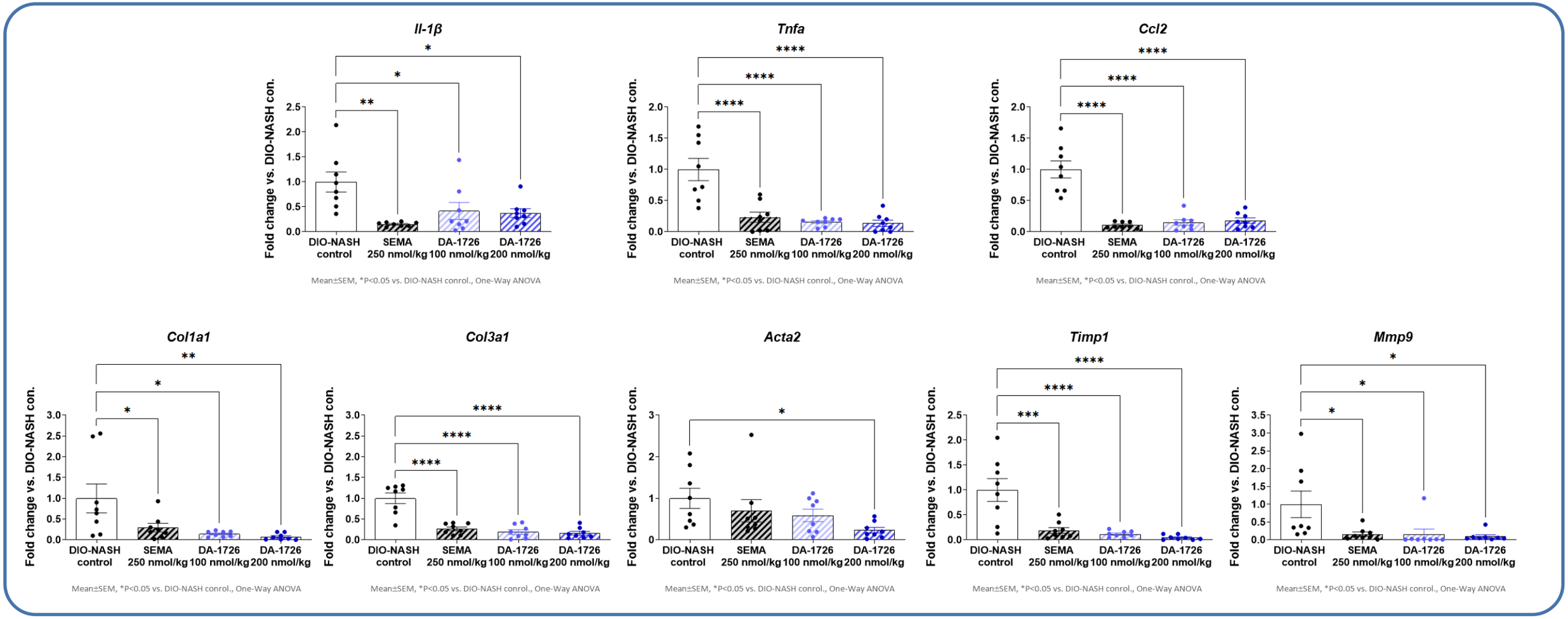




- Abbreviation: SEMA, Semaglutide

RESULTS – 3. Gene Expression in Liver Tissue

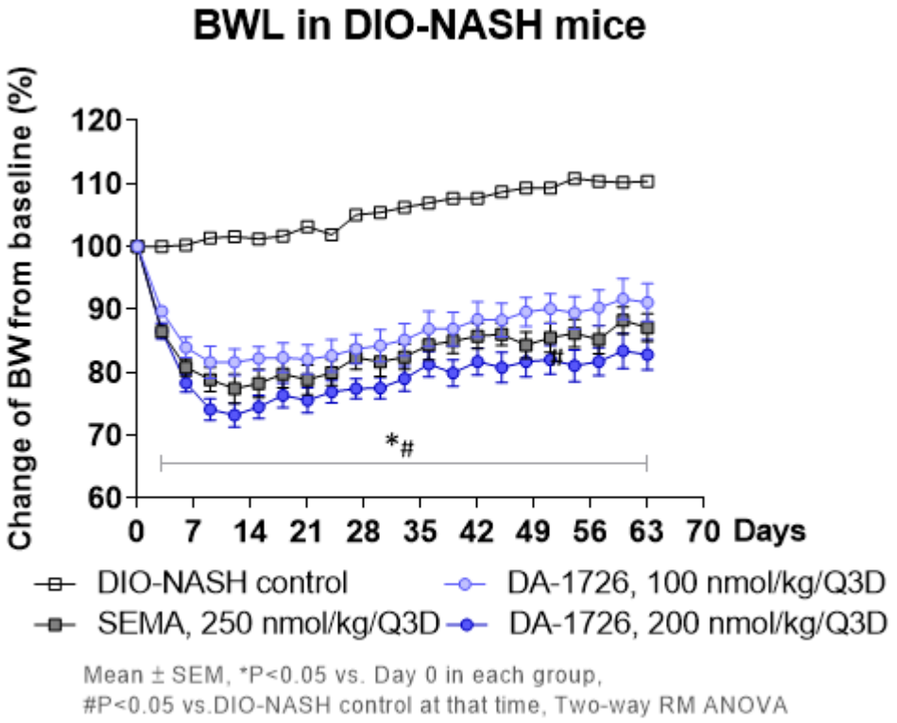
- **The expression of inflammation (*Il-1β*, *Tnfa*, and *Ccl2*) and fibrosis (*Col1a1*, *Col3a1*, *Acta2*, *Timp1*, and *Mmp9*) related genes was significantly decreased by DA-1726 treatment**

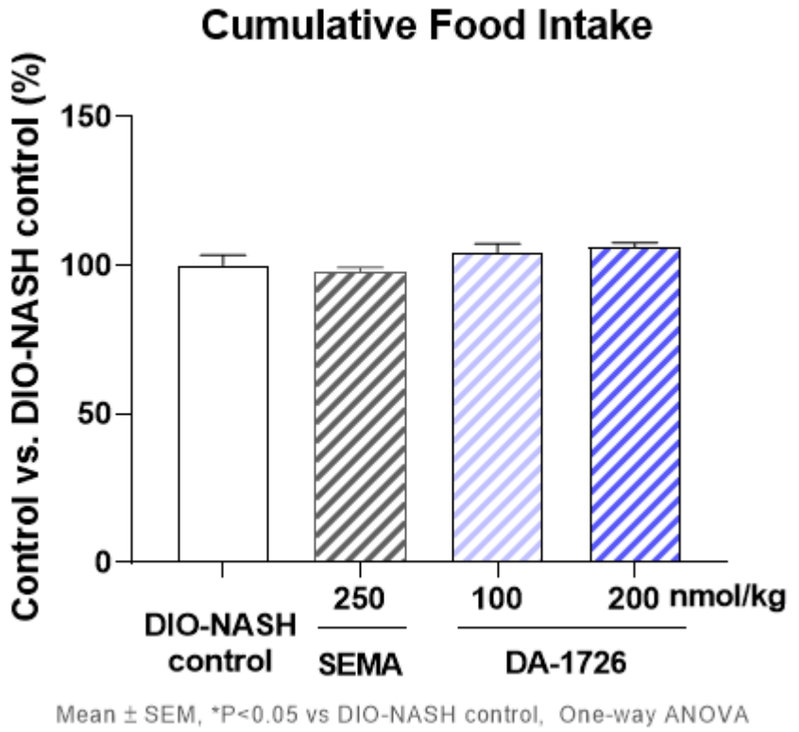


- Abbreviation: SEMA, Semaglutide

RESULTS – 4. Body Weight Loss

- **DA-1726 significantly reduced body weight and DA-1726 low-dose group showed higher anti-NASH effects despite lower body weight loss compared to semaglutide**





- Abbreviation: SEMA, Semaglutide

SUMMARY

- DA-1726 is a dual agonist with balanced activity against GLP-1 and glucagon receptors.
- In DIO-NASH mice, DA-1726 significantly decreased plasma clinical chemistry parameters (ALT, AST, ALP, and T-BIL) and hepatic fat accumulation.
- In histopathological analysis of steatosis, lobular inflammation, and ballooning in the liver, DA-1726 showed an excellent improvement effect compared to semaglutide NAFLD Activity Score. The improvement of hepatic fibrosis by DA-1726 was also observed.
- In the liver tissue, the expression of inflammation and fibrosis-related genes was significantly decreased by DA-1726 treatment. In particular, the DA-1726 low-dose group showed a higher efficacy despite lower weight loss compared to semaglutide. This is thought to be a result of the dual actions of DA-1726 to GLP-1 and glucagon receptors.
- Taken together, our findings suggest that DA-1726 has a therapeutic potential for NASH in addition to obesity and type 2 diabetes.