Bimagrumab prevents semaglutide-induced loss of lean mass in diet-induced obese mice

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Background & Aim

Rapid weight loss promoted by incretin-based therapies, including semaglutide (GLP-1 receptor agonist), can result in concomitant loss of muscle mass (sarcopenia). Maintaining msucle mass is beneficial for metabolic health, functionality and quality of life. The present study aimed to assess if Bimagrumab (human anti-activin II-receptor antibody) can prevent loss of lean body mass during semaglutide-induced weight loss in diet-induced obese (DIO) mice.

Methods

Male C57BL/6JRj mice were fed a high-fat diet (60 kcal-% fat) for 26 weeks. DIO mice were randomized and stratified to treatment based on body weight (n=10 per group). Semaglutide (30 nmol/kg, QD), Bimagrumab (human monoclonal antibody, 20 mg/kg, QW) or corresponding vehicle was administered (SC) for 4 weeks (see Fig. 1). Vehicle-dosed age-matched chow-fed mice served as a lean controls. Study endpoints included body weight, food intake, muscle weight, whole-body fat/lean mass (EchoMRI), estimated whole-body muscle mass (D3-creatine dilution assay), forelimb grip strength and skeletal muscle histology.

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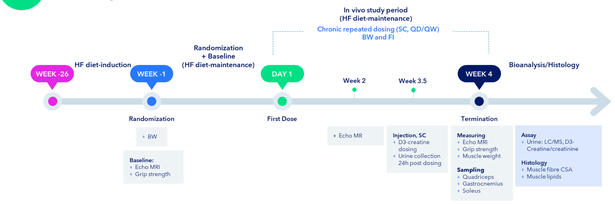
1 Study outline



Group	Group name	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing Concentration
1	Vehicle – Lean	10	Vehicle + Vehicle	SC+SC	QD+QW	0+0
2	Vehicle - DIO	10	Vehicle + Vehicle	SC+SC	QD+QW	0+0
3	Semaglutide	10	Semaglutide + Vehicle	SC+SC	QD+QW	30 nmol/kg + 0
4	Bimagrumab	10	Vehicle+ Bimagrumab	SC+SC	QD+QW	0 +20 mg/kg
5	Semaglutide + Bimagrumab	10	Semaglutide + Bimagrumab	SC+SC	QD+QW	30 nmol/kg + 20 mg/kg

Figure 1. Study outline.

2 Body weight, food intake and muscle weight

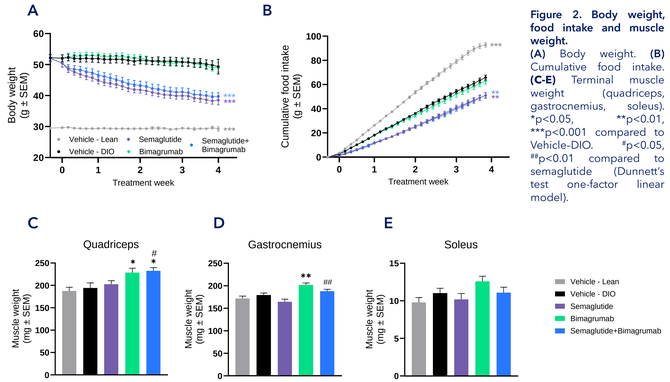


Figure 2. Body weight, food intake and muscle weight. **(A)** Body weight. **(B)** Cumulative food intake. **(C-E)** Terminal muscle weight (quadriceps, gastrocnemius, soleus). *p<0.05, **p<0.01, ***p<0.001 compared to Vehicle-DIO. #p<0.05, ##p<0.01 compared to semaglutide (Dunnett's test one-factor linear model).

3 Body composition

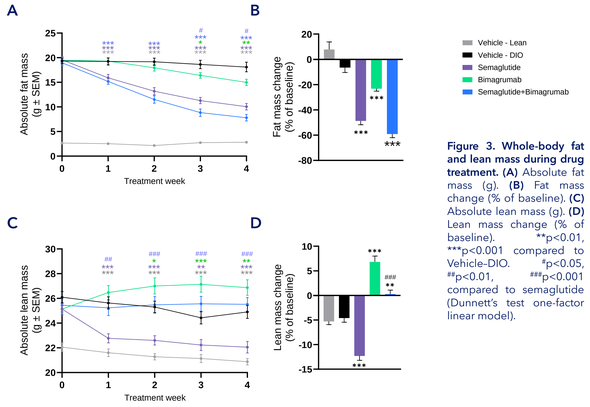


Figure 3. Whole-body fat and lean mass during drug treatment. **(A)** Absolute fat mass (g). **(B)** Fat mass change (% of baseline). **(C)** Absolute lean mass (g). **(D)** Lean mass change (% of baseline). **p<0.01, ***p<0.001 compared to Vehicle-DIO. #p<0.05, ##p<0.01, ###p<0.001 compared to semaglutide (Dunnett's test one-factor linear model).

4 Muscle mass and functionality

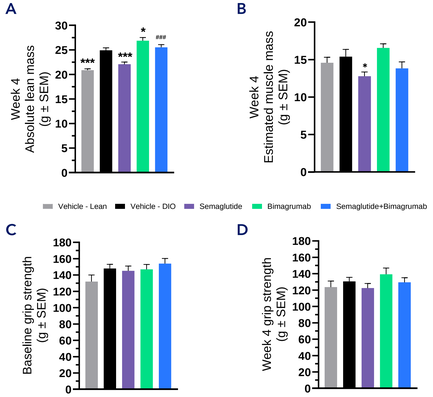
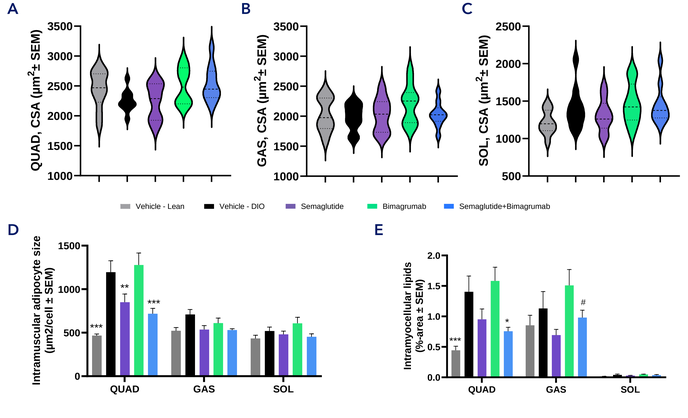


Figure 4. Estimated muscle mass and forelimb grip strength. **(A)** Terminal lean mass (MRI). **(B)** Estimated muscle mass at termination (D3-creatine dilution assay). **(C)** Baseline grip strength. **(D)** Grip strength at study termination. *p<0.05, ***p<0.001 compared to Vehicle - DIO, ###p<0.001 compared to semaglutide.

5 Muscle histology



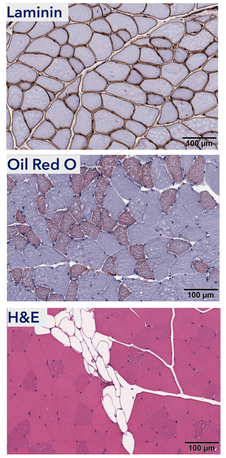


Figure 5. Histomorphometric assessment of muscle fiber cross-sectional area (CSA, proxy for plasticity) and lipid content. Muscle fiber CSA (µm², laminin staining) for **(A)** quadriceps (QUAD), **(B)** Gastrocnemius (GAS) and **(C)** Soleus (SOL). **(D)** Quantification of intramuscular adipocyte size (µm², H&E staining). **(E)** %-area of intramyocellular lipids (Oil Red O staining). *p<0.05, **p<0.01, ***p<0.001 compared to Vehicle – DIO, #p<0.05 compared to semaglutide.

Conclusion

- Semaglutide reduces body weight in DIO mice by reducing both fat and lean mass
- Bimagrumab as combination therapy with Semaglutide prevents loss of lean mass with preserved body weight loss
- Bimagrumab monotherapy increases lean mass, but not muscle strength, in DIO mice
- Semaglutide and Bimagrumab does not influence skeletal muscle fiber plasticity in DIO mice
- Semaglutide, but not Bimagrumab, reduces muscle lipid accumulation in DIO mice

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