Continuous Semaglutide Infusion Impacts Female Mouse Musculoskeletal Tissue During Immobilization Without Changing Food Intake or Body Weight

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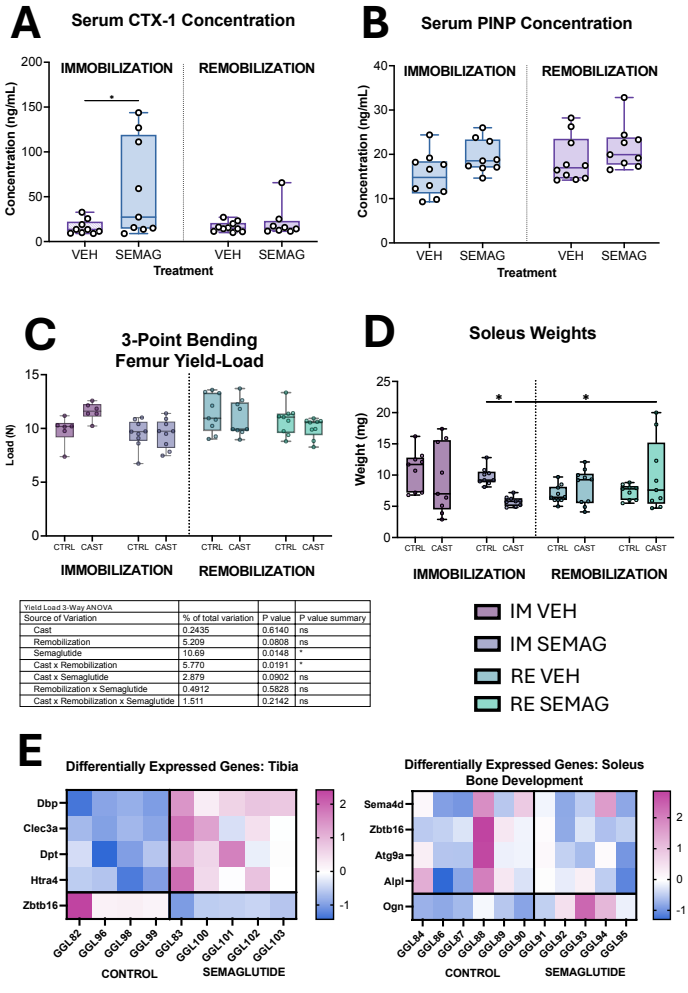
INTRODUCTION: Semaglutide (Ozempic®, Wegovy®), a GLP-1 receptor agonist, is increasingly being prescribed to a growing number of patients for the treatment of type 2 diabetes and for weight loss. Weight loss leads to a loss of bone and muscle volume. Immobilization (disuse) also leads to resorption of both bone and muscle tissue. We therefore hypothesized that semaglutide treatment would exacerbate the loss of bone and muscle mass with immobilization and would interfere with bone and muscle recovery during subsequent remobilization.

METHODS: Alzet osmotic pumps were surgically implanted in female C57BL/6J mice (n=40; 14 weeks old) 14 days before immobilization. The pumps delivered either semaglutide in 0.9% saline (10 mg/kg/day, n=20) or vehicle (0.9% saline, n=20). All mice were immobilized for 14 days via a single leg cast. After 14 days, mice were euthanized or had their cast removed and were reloaded for 14 days. Body composition and bone mineral density (BMD) were measured weekly via dual-energy x-ray absorptiometry (DEXA). Mice were fed standard chow, with food intake and body weight monitored biweekly. After euthanasia, the gastrocnemius and soleus were dissected and weighed. Femurs were imaged with micro-computed tomography (μCT 35, SCANCO Medical AG) with 6 μm nominal voxel size; both cortical bone (mid-diaphysis) and trabecular bone (metaphysis and epiphysis) were analyzed to determine bone microstructural outcomes. Femurs were also mechanical tested via 3-point bending. Serum samples were analyzed via ELISA for PINP and CTX-1 concentrations. Bulk RNA sequencing of immobilized limb tibias and solei was conducted. Female mice were chosen given the societal pressures on females to use weight loss medications. Females are more likely to be marketed these interventions and are more likely to be prescribed semaglutide for weight loss than males. All animal work and procedures were approved by the UC Davis Institutional Animal Care and Use Committee. 3-Way ANOVA was used to investigate drug treatment, immobilization, time, and interactions.

RESULTS SECTION: Cortical and trabecular bone microarchitecture did not differ after 14 days of casting between the two treatment groups. Serum CTX-1 concentrations increased in semaglutide-treated animals after immobilization (Fig. 1A p=0.022). Serum P1NP concentrations increased with semaglutide treatment (Fig. 1B p=0.025) but had no interaction with immobilization or reloading. Semaglutide reduced femur mechanics, including yield load (Fig.1C p=0.015), max load (p=0.42), work to yield (p=0.021), and trended towards decreasing yield-displacement (p=0.075) and fracture load (p=0.084). Semaglutide treatment caused significant muscle loss with immobilization in the soleus (Fig. 1D p=0.036), gastrocnemius (p<0.001), plantaris (p=0.008)). Vehicle mice only saw loss of muscle mass in the gastrocnemius (p<0.001). Muscle mass was recovered in all mice except in the gastrocnemius of both vehicle and semaglutide-treated groups. Gene expression of Zbtb16 was downregulated in the bone and muscle of immobilized limbs (Fig. 1E log2 fold change = -1.66, adj p<0.001). Several other bone development genes were also differentially expressed (Fig, 1E). Mouse body weight and chow consumption remained unchanged in semaglutide treated mice compared to controls.



Yield Load 3-Way ANOVA			
Source of Variation	% of total variation	P value	P value summary
Cast	0.2435	0.6140	ns
Remobilization	5.209	0.0808	ns
Semaglutide	10.69	0.0148	*
Cast x Remobilization	5.770	0.0191	*
Cast x Semaglutide	2.879	0.0902	ns
Remobilization x Semaglutide	0.4912	0.5828	ns
Cast x Remobilization x Semaglutide	1.511	0.2142	ns

Figure 1. *Bone and muscle changes in response to semaglutide treatment (SEMAG) and casting (CAST). *: p <0.05.*

DISCUSSION: Bone resorption markers increase with immobilization, while bone formation markers increase overall with semaglutide treatment but are not affected by immobilization. Semaglutide had a negative effect on femoral fracture mechanics, but not microarchitecture at a 14-day timepoint. Expression of Zbtb16, an important gene for the prevention of osteoporosis, was significantly downregulated in both bone and muscle during immobilization with semaglutide treatment. During immobilization, semaglutide-treated mice lost significantly more muscle mass in their immobilized leg compared to vehicle-treated mice. Semaglutide-treated mice did not lose body weight or reduce chow consumption compared to the vehicle-treated group. The observed changes, therefore, cannot be attributed to secondary effects of acute weight loss. The use of an osmotic pump instead of twice daily gavage or injection could explain the lack of weight loss, as continuous release semaglutide concentrations may cause less gastrointestinal distress than higher doses seen in other administration methods. Trends in bone and muscle loss of mass and function warrant longer term investigations into the effect of semaglutide on musculoskeletal health with and without immobilization.

SIGNIFICANCE: Understanding the impact of this medication on musculoskeletal function will help clarify whether treatment of patients who require immobilization with using Ozempic®, Wegovy®, and other GLP-1 receptor agonists could exacerbate negative side effects.

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