Protective Effects of HM17321, a novel UCN2 analog, on Obesity-associated Musculoskeletal Diseases in Mouse models

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Abstract

Introduction and Objective: Obesity increases the risk of musculoskeletal diseases including osteoarthritis (OA) and osteoporosis (OP). Weight-loss medications are shown to improve musculoskeletal outcomes by reducing joint load, but lean mass preservation is also crucial for stabilizing joints, protecting bone density and mitigating frailty and functional decline. HM17321 is a novel CRFR2 selective UCN2 analog and has been demonstrated to improve weight loss quality by enhancing both muscle hypertrophy and lipolysis in obese mice. In this study, we aim to evaluate therapeutic potential of HM17321 on obesity-related OA and OP.

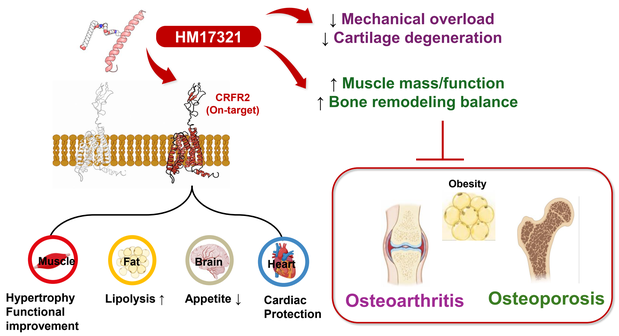
Methods: We utilized two distinct in vivo models: the surgical DMM-induced OA and OVX-induced OP in HFD-fed mice. HM17321 or semaglutide (were subcutaneously administered in HFD/DMM mice for 6 weeks and then motor function and histology of cartilage were assessed. In a second study, HFD/OVX mice were treated with HM17321 or semaglutide for 8 weeks and then serum markers and muscle function were evaluated.

Results: HM17321 consistently led to a significant fat reduction and increase in lean and skeletal muscle mass in both HFD/DMM and HFD/OVX mice. Notably, HM17321 significantly improved weight bearing (92.1% vs. 80.5%, vehicle; 99.6%, Sham vehicle) and locomotor activity in HFD/DMM mice. OARSI score for joint cartilage was lowered by HM17321 (7.3 vs. 9.6, vehicle; 0.6, Sham vehicle). In HFD/OVX mice, HM17321 significantly decreased serum CTX-1/P1NP ratio (0.11 vs. 0.20, vehicle; 0.14, Sham vehicle) suggesting a shift toward a more balanced bone remodeling. Moreover, functional improvement of skeletal muscle was observed in HM17321-treated HFD/OVX mice, compared to semaglutide

Conclusion: HM17321 resulted in a significant fat reduction simultaneously increasing lean mass in obesity-associated OA and OP mice. These favorable changes in body composition, beyond simple weight loss, may contribute to more effectively improve obesity-associated OA and OP.

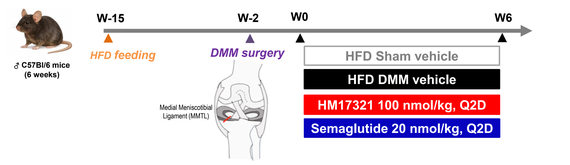
Background

HM17321, a novel long-acting CRFR2 selective UCN2 analog, is optimally designed to selectively reduce fat while simultaneously increasing muscle mass during weight loss, maximizing weight loss quality (WLQ) and metabolic improvement.



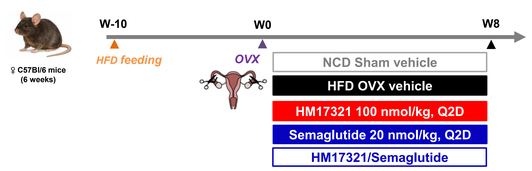
Methods

Study 1. Osteoarthritis mouse model (HFD and Destabilization of the Medial Meniscus-induced)



√ *Parameters: Body weight and body composition, behavior testing (pain-related)*
Histopathology of joints

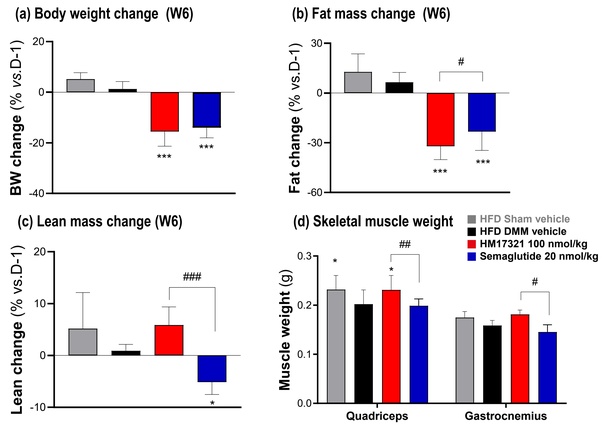
Study 2. Osteoporosis mouse model (HFD and Ovariectomy)



√ *Parameters: Body weight and composition, behavior testing (grip strength, wire hang)*
Biomarker for bone turnover

Weight loss and Increased muscle mass in OA mice

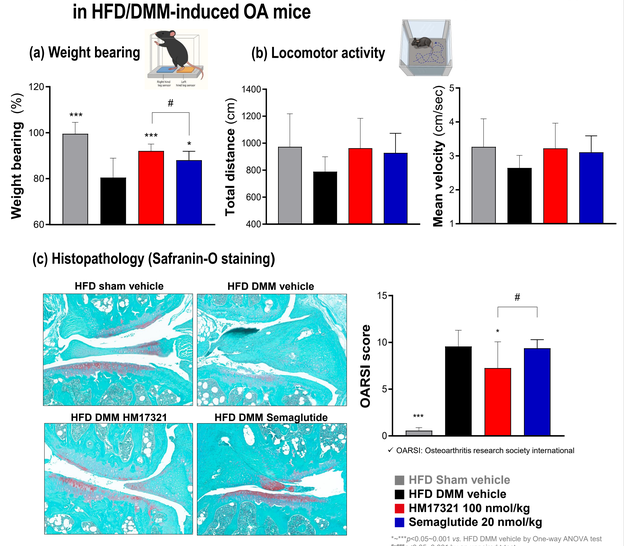
Figure 1. Effect of HM17321 on body composition and skeletal muscle weight in HFD/DMM-induced osteoarthritis (OA) mice



➢ HM17321 enhanced weight loss quality by reducing fat and promoting lean and skeletal mass gain, unlike semaglutide which leads to lean mass loss.

Improved functional outcomes and Joint histopathology

Figure 2. Effect of HM17321 on functional impairment and joint pathology in HFD/DMM-induced OA mice

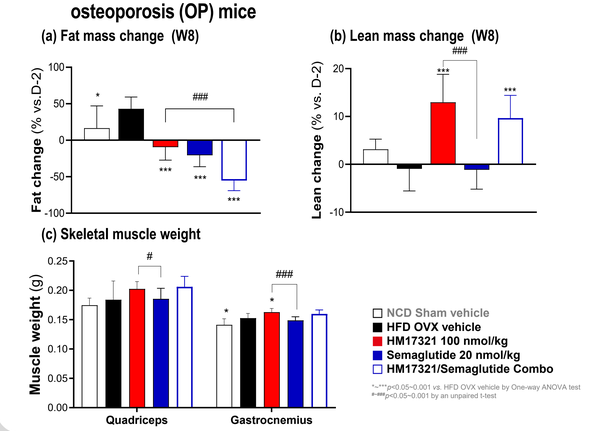


*-***p<0.05~0.001 *vs.* HFD DMM vehicle by One-way ANOVA test
#-###p<0.05~0.001 by an unpaired t-test

➢ HM17321 significantly attenuated OA-associated pain behaviors, as evidenced by weight-bearing and locomotor activity, and reduced histopathological joint degeneration.

Body Recomposition and Muscle Gain in OP mice

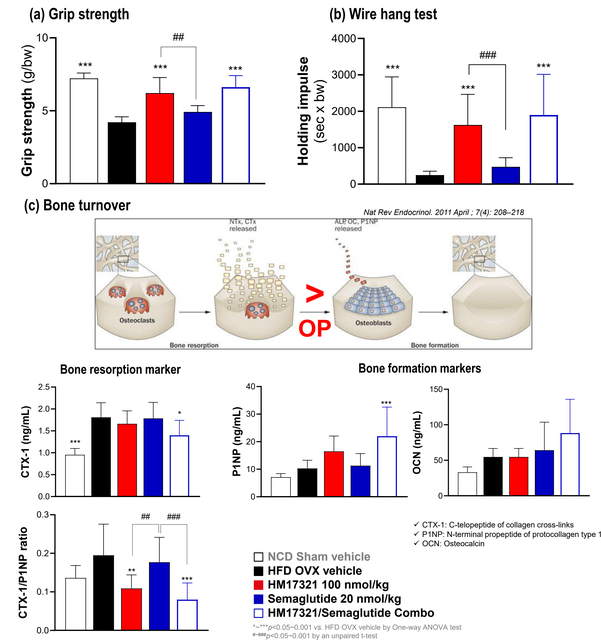
Figure 3. Effect of HM17321 on body composition in HFD/OVX-induced osteoporosis (OP) mice



*-***p<0.05~0.001 vs. HFD OVX vehicle by One-way ANOVA test
#-###p<0.05~0.001 by an unpaired t-test

Enhanced muscle function and Balanced bone turnover

Figure 4. Effect of HM17321 on skeletal muscle function and bone turnover in HFD/OVX-induced OP mice



*-***p<0.05~0.001 vs. HFD OVX vehicle by One-way ANOVA test
#-###p<0.05~0.001 by an unpaired t-test

➢ HM17321 significantly increased lean and skeletal muscle mass and improved physical performance as demonstrated by grip strength and wire hang tests in obesity-associated OP mice. Notably, HM17321 restored CTX-1/P1NP ratio to normal levels. Combination treatment of HM17321 and semaglutide further reduced fat mass while enhancing bone formation activity.

Concluding Remarks

- HM17321 significantly decreased fat mass and increased lean mass in both OA and OP models. HM17321 improved OA-associated symptoms such as impaired weight bearing and locomotor activity. Histologically, joint degeneration was also improved by HM17321. These improvements were greater than those observed with semaglutide.
- In the OP model, HM17321 enhanced muscle mass, physical performance and balance of bone remodeling. HM17321/semaglutide combination produced grater fat mass reduction together with improvements in physical performance and bone turnover markers. From these findings, HM17321 could mitigate obesity-associated bone health risks in part through weight loss and simultaneous increase in muscle mass.
- Hanmi's posters for HM17321, LA-UCN2: 1783-P, 2537-P, 2538-P, 2579-P, 2872-LB, 3078-LB
- Hanmi's posters for HM500197, LA-MSTN: 3073-LB