Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in the obese-osteoporosis rodent model

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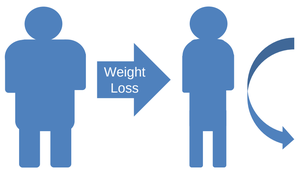
BACKGROUND

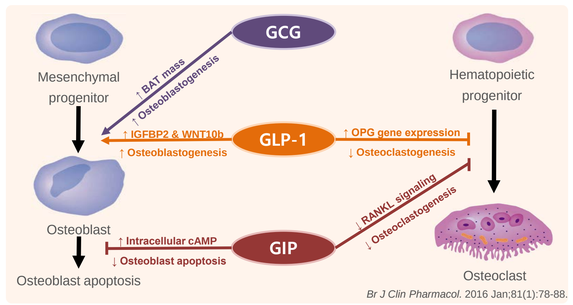
- **Increased fracture risk associated to weight loss[1]**



Bone mass loss
↓ Mechanical effect
↓ Insulin and IGF-1
↓ Estrogen, Adiponectin and Ghrelin
↓ Calcium absorption

Increased Fall Risk
Disorder of bone quality
Mineralization disorder
Bone mass loss

- **Bone homeostasis effects of GCG[2], GLP-1[3] and GIP[4]**



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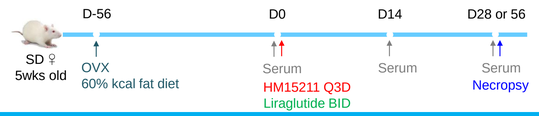
AIMS

This study investigated whether treatment with HM15211 prevents bone loss under a severe weight loss condition, and the underlying mechanism of action.

METHODS

- To investigate MoA for bone protection of HM15211, MC3T3-E1 cells were treated with HM15211. Osteoblast differentiation related markers (RUNX2, OCN, ALP and Col1α) were analyzed using real-time PCR. Additionally, collagen protein expression change and anti-apoptotic effect were evaluated using commercial kit.

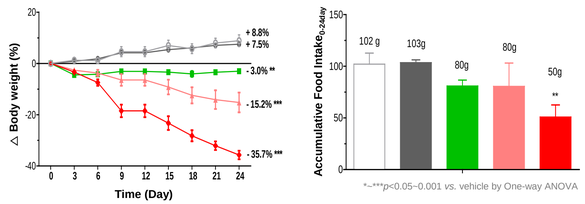
- Diet induced obesity (DIO) osteoporosis rat model was induced by surgical oophorectomy (OVX) and fed 60% kcal fat diet to immatured 5 weeks old female sprague dawley (SD) rats for 8 weeks. Serum levels of bone biochemical markers (Glu-OC ; Glu-Osteocalcin, OPG ; Osteoprotegerin and PINP ; Procollagen type I propeptides) were measured by commercial ELISA kits. BMD (Bone mineral density) of femurs were monitored using a high resolution in vivo μ-CT system (n = 7 /group). Food restricted group was supplied limited amount of daily food to be had same weight loss with HM15211 2.2 nmol/kg treated group.



RESULTS

Reduction of body weight and food intake

Figure 1. Body weight change and accumulative food intake



*~***p<0.05~0.001 *vs.* vehicle by One-way ANOVA

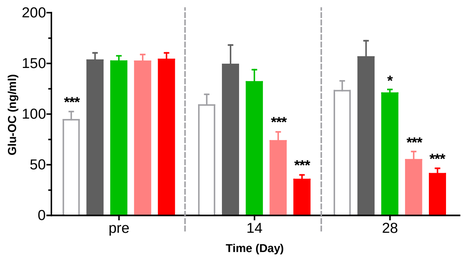
➢ HM15211 administration significantly decreased body weight and food intake, respectively.

Sham vehicle, Q2D
OVX vehicle, Q2D
OVX Liraglutide 25 nmol/kg, BID (3 mg/day in human)
OVX HM15211 2.2 nmol/kg, Q2D (4 mg/week in human)
OVX HM15211 4.4 nmol/kg, Q2D (8 mg/week in human)

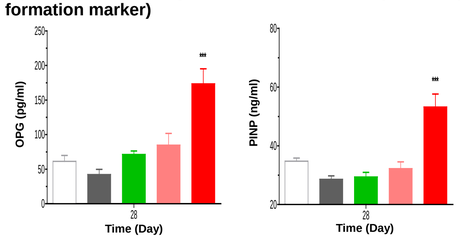
Improvement of bone biochemical markers

Figure 2. Serum levels of Glu-OC, OPG and PINP

(a) Glu-OC (bone resorption marker)



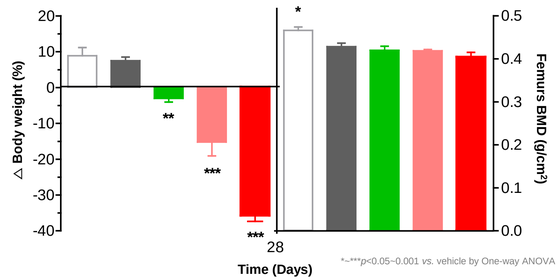
(b) OPG (osteoclastogenesis inhibition marker) & PINP (bone formation marker)



➢ Bone bio chemical markers (Glu-OC, OPG and PINP) were dose dependently improved on HM15211 dosing group, respectively.

Prevention of BMD loss following weight loss

Figure 3. Weight loss and femurs BMD



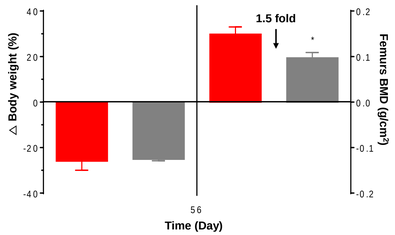
*~***p<0.05~0.001 *vs.* vehicle by One-way ANOVA

➢ Even in a severe weight loss condition, HM15211 prevented BMD loss of femurs

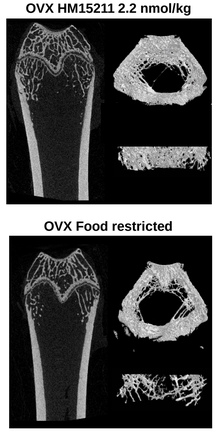
Protection of bone health in same weight loss

Figure 4. Bone health profiles while weight loss matching

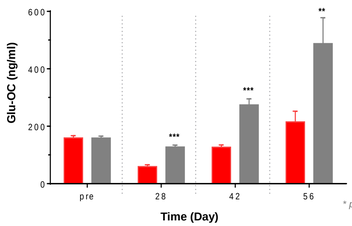
(a) Weight loss and femurs BMD



(b) μ-CT image of Femurs



(c) Glu-OC (bone resorption marker)



* $p<0.05$ *vs.* food restricted group by *t*-Test

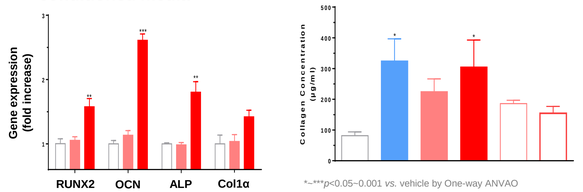
OVX HM15211 2.2 nmol/kg, Q2D (4 mg/week in human)
OVX Food restricted

➢ During the same weight loss, HM15211 prevented the decline of bone health

MoA studies for bone protection

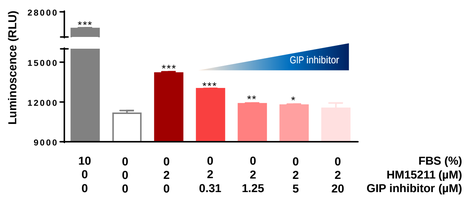
Figure 5. Bone protection mechanism in MC3T3-E1 cell

(a) Osteoblast differentiation marker genes & Collagen expression in conditioned media



*~***p<0.05~0.001 *vs.* vehicle by One-way ANVAO

(b) Inhibition of osteoblast apoptosis



➢ HM15211 improved osteoblast differentiation and showed anti-apoptotic effect. Additionally, GIP antagonist reversed the beneficial effect of HM15211 on bone protection.

CONCLUSIONS

- **Lower serum level of Glu-OC and higher serum levels of OPG and PINP were observed compared with those of vehicle and liraglutide treated groups in obese-osteoporosis rats model.**
- **HM15211 showed comparable BMD of femurs compare to vehicle while it showed greater weight loss compared to liraglutide in obese-osteoporosis rats model.**
- **HM15211 led to significant increase in collagen and Gla-OC expression, which were blunted by inhibition of GIPR-mediated signaling in osteoblast cell.**
- **These results suggest that HM15211 might provide potent weight loss without bone loss**

REFERENCES

1. Francisco J. A. de Paula and Clifford J. Rosen, Arq Bras Endocrinol Metabol. 2010 Mar;54(2):150-7.
2. Francesc Villarroya et al., Nat Rev Endocrinol. 2017 Jan;13(1):26-35.
3. Guojing Luo et al., Br J Clin Pharmacol. 2016 Jan;81(1):78-88.
4. Katsushi Tsukiyama et al., Mol Endocrinol. 2006 Jul;20(7):1644-51.

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