Sexual Dimorphism of Treatment Response to the Low-dose Semaglutide in the Mice Osteoarthritis Model

Mingde Cao[1,2], Xueyou Zhang[1], Run Huang[2], Kevin Jin[2], Patrick Shu-Hang Yung[1,2], Michael Tim-Yun ONG[1,2]
[1] Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR
[2] Center for Neuromusculoskeletal Restorative Medicine (CNRM), The Chinese University of Hong Kong, Hong Kong SAR
Email of Presenting Author: mingdecao@link.cuhk.edu.hk

Disclosures: Mingde Cao (N), Xueyou Zhang (N) Run Huang (N) Kevin Jin (N) Patrick Shu-Hang Yung (N) Michael Tim-Yun ONG (N)

INTRODUCTION: Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, are emerging as potential disease-modifying therapies for osteoarthritis (OA). However, their efficacy independent of weight loss and their sex-specific effects on joint pain and pathology remain poorly understood. This study aimed to investigate the sexually dimorphic therapeutic responses to a low, non-weight-reducing dose of semaglutide in a surgical mouse model of OA.

METHODS: Male and female C57BL/6J mice underwent Destabilization of the Medial Meniscus (DMM) surgery to induce OA and received weekly subcutaneous injections of either vehicle or a low dose of semaglutide (100 ng/g) for 7 weeks (n=9/group). Therapeutic efficacy was assessed by evaluating pain-related behaviours (von Frey test), locomotor activity (open-field test), and gait (CatWalk analysis). At the 8-week endpoint, joint structural changes were quantified using Safranin-O staining for cartilage and synovium (OARSI and synovitis scores) and micro-computed tomography (µCT) for subchondral bone and peri-articular ossification. Additional single-cell sequencing of the synovium was performed in male mice (DMM vs. GLP1; n = 6).

RESULTS SECTION: A sexual dimorphism in treatment response was observed. In female mice, semaglutide provided superior functional and analgesic benefits. It significantly reversed mechanical allodynia as measured by the von Frey test and normalised pain-related gait patterns, effects that were minimal in males. Conversely, male mice exhibited more robust structural protection. Semaglutide treatment in males significantly attenuated cartilage degradation (mean OARSI score difference GLP1 vs. DMM: 1.33, p= *0.014*), reduced synovitis (p<0.05), and mitigated DMM-induced intra-articular ossification of the meniscus and synovium (*p= 0.045*). These structural benefits were not significant in female mice. The expression of *Pacl8* in inflammatory monocyte subpopulations in the synovium of male mice was significantly downregulated.

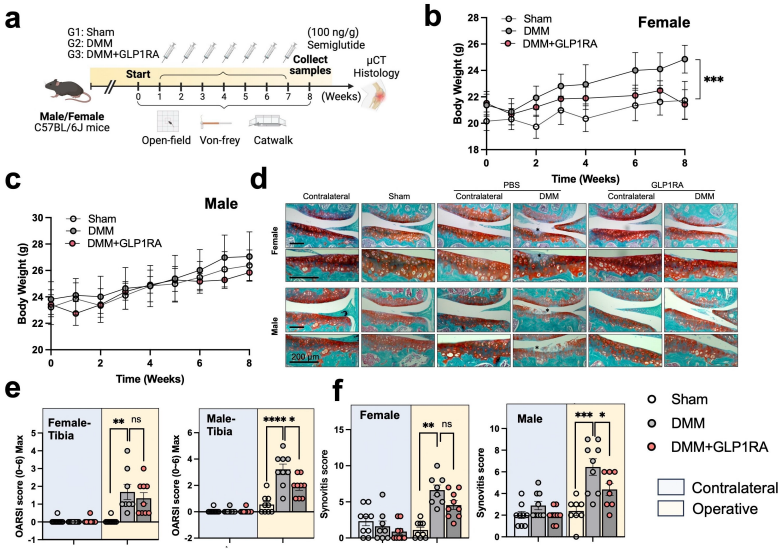

Fig 1. Semaglutide elicits sex-specific improvements in cartilage degeneration and synovitis in a surgical mouse model. (**a**) Schematic diagram illustrating the experimental timeline. Graphical representation of body weight changes over the 8-week experimental period for (**b**) female and (**c**) male mice. (**d**) Representative Safranin O and Fast Green staining for female (upper panel) and male (lower panel) mice. Asterisks (*) highlight areas of cartilage lesions. Scale bar = 200 µm. (**e**) Quantification of cartilage degradation via OARSI scoring system on the tibial plateau for both female and male mice. (**f**) Quantification of synovitis scores fo female and male mice. Data are presented as mean ± SD, with each dot representing an individual animal (n=8~9). Statistical significance was determined by one-way ANOVA with Tukey's multiple comparison tests. (ns = not significant; **p < 0.01; ***p < 0.001; ****p < 0.0001).

DISCUSSION: Low-dose semaglutide treatment results in a significant sexual dimorphism in therapeutic response in a murine OA model. These effects occurred without weight reduction, providing strong evidence that GLP-1RA can function through direct, weight-independent mechanisms. The downregulation of *Pacl8* in synovial monocytes further supports a direct molecular mechanism for inflammation control. In contrast, the superior analgesia in females, despite minimal structural change, points toward alternative mechanisms, possibly involving the modulation of central or peripheral pain pathways, which are also known to express GLP-1 receptors.

SIGNIFICANCE/CLINICAL RELEVANCE: These findings highlight the necessity of considering sex as a critical biological variable when developing GLP-1 receptor agonist therapies for OA.

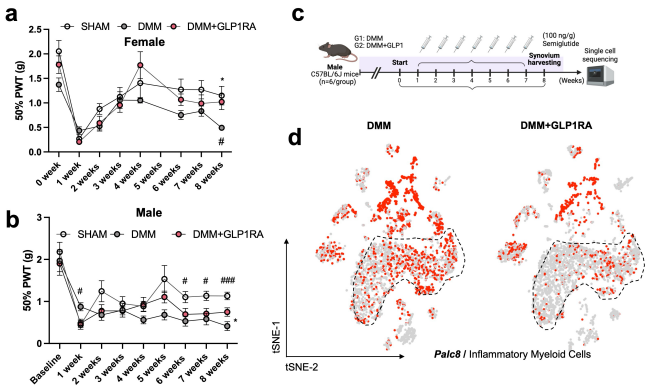

Fig 2. Semaglutide provides superior pain relief in female mice. Mechanical sensitivity of (**a**) female group and (**b**) male mice was measured by von Frey filament testing. (**c**) schematic diagram illustrating the experimental time frame of single cell sequencing (n= 6/group). (**d**) Feature plot of the *Palc8* expression in the inflammatory myeloid cells subpopulation in both DMM and GLP1RA groups. Data are presented as mean ± standard deviation, with each dot representing an individual animal. Line graphs represent mean ± S.E.M. Statistical significance was determined by two-way ANOVA and sidak holmes post hoc test. (*p < 0.05, **p < 0.01 compared to the Sham group; #p < 0.05, ##p < 0.01 compared to the DMM group).

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