Protective Effects Of Intra-Articular Formulated Liraglutide In Osteoarthritis: Preclinical Studies

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INTRODUCTION & AIM

Osteoarthritis (OA) is a degenerative joint disease affecting millions of individuals worldwide. Its development has been reported to be associated with cartilage degradation and inflammatory responses leading to pain, swelling and reduced function. Osteoarthritis is a serious and frequent disease. It affects 315 million people worldwide, making it the leading cause of functional disability. This disease is a burden that can lead indirectly to death.

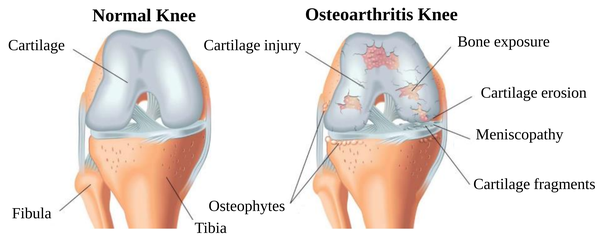


***Fig. 1**: Knee joint degradation in osteoarthritis (https://www.local-physio.co.uk/articles/general/osteoarthritis/)*

Liraglutide, a Glucagon-Like-Peptide 1 Receptor (GLP-1R) agonist, is clinically used as a subcutaneous treatment for type 2 diabetes. Interestingly, immunomodulatory and anti-inflammatory properties of the GLP-1 pathway have been recently described in various diseases but its role in the pathogenesis of OA remains to be elucidated.

Thus, the goal of this present work was to evaluate the local effects of Liraglutide in *in vitro* and *in vivo* models of OA by evaluating surrogate markers of inflammation and cartilage matrix proteolysis, cartilage degradation and pain.

ASSESSING

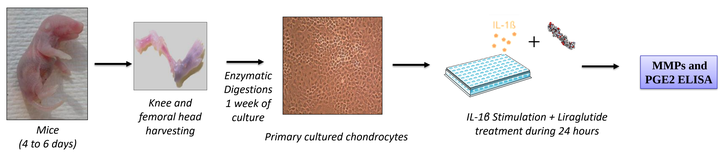


***Fig. 2**: IL-1β-(2ng/ml) stimulated mouse articular chondrocytes were treated with different concentrations (3, 10 and 50nM) of Liraglutide for 24h. Production of matrix metalloproteinases (MMPs) and prostaglandin E2 (PGE2) in supernatant was measured by ELISA.*

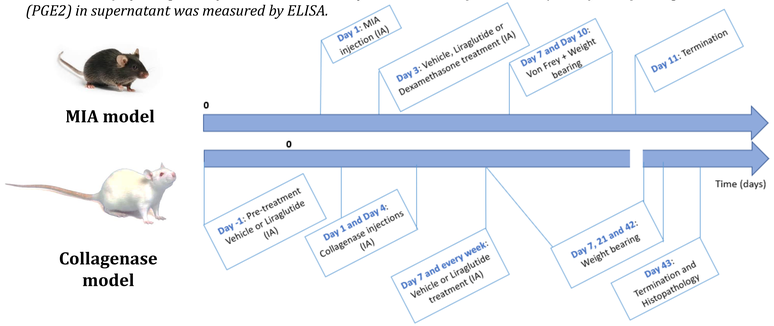


***Fig. 3**: Intra-articular (IA) injections of formulated Liraglutide or vehicle were performed in two chemically-induced inflammatory knee OA models: the mouse monosodium iodoacetate (MIA) model and the rat collagenase type II model (IA injection into the right knee). Paw withdrawal threshold and weight bearing distribution were performed for pain behavior assessment. Histopathological analyses (OARSI score) were conducted blindly by one observer in the rat collagenase OA model for evaluating cartilage degradation.*

RESULTS

(1) Liraglutide decreases inflammatory and catabolic mediators production in IL1-β-stimulated mouse chondrocytes

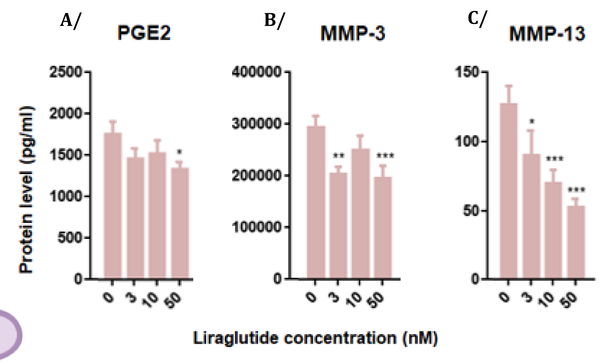


***Fig. 4**: **A/** Liraglutide significantly reduced the IL-1β-induced production of PGE2 (1341pg/ml ± 86pg/ml vs 1766pg/ml ± 145pg/ml for vehicle, p≤0.05, 50nM dose) and **B/** cartilage matrix catabolic enzymes MMP-3 (294 000pg/ml ± 23 000pg/ml for vehicle vs 204 000pg/ml ± 15 000pg/ml, p≤0.01, 3nM dose; vs 197 000 ± 23 000 pg/ml, p≤0.001, 50nM dose) and **C/** MMP-13 with a dose response (127pg/ml ± 14pg/ml for vehicle vs 90pg/ml ± 18pg/ml, p≤0.01, 3nM dose; vs 70pg/ml ± 10ng/ml, p≤0.001, 10nM dose; vs 52pg/ml ± 6ng/ml, p≤0.001, 50nM dose) in murine chondrocytes.*

(2) Liraglutide has analgesic effect in MIA induced model in mice

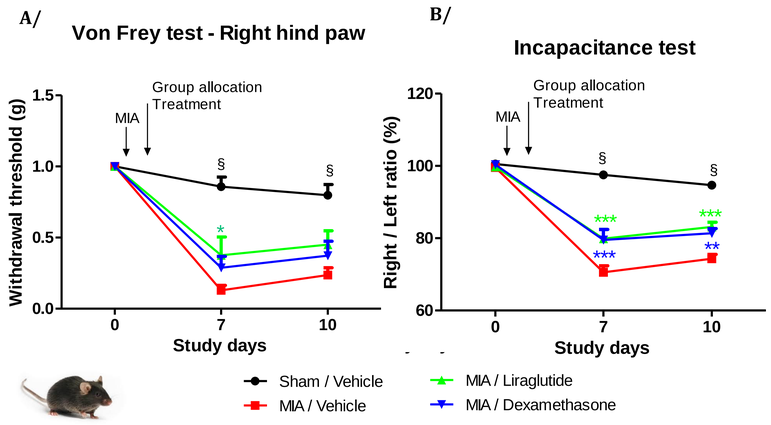
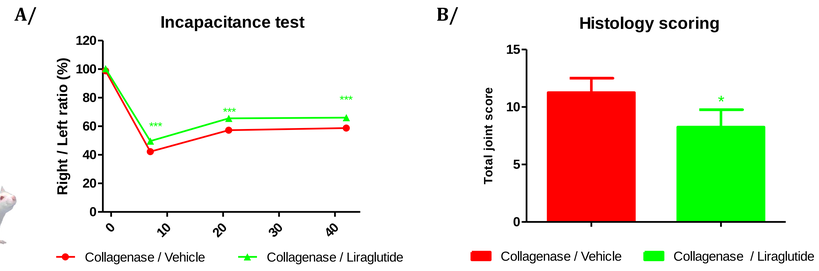


***Fig. 5**: In mouse MIA model (0,75mg/mouse, IA injection on Day 1), **A/** a single IA injection of formulated Liraglutide at day 3 increased significantly paw withdrawal threshold (0.37g ± 0.39g vs 0.13g ± 0.11g for vehicle, p≤0.05, day 7) and **B/** improved weight distribution to the affected limb (80% ± 7% at day 7 and 83% ± 4% at day 10, p≤0.001) compared to vehicle (71% ± 6% at day 7 and 74% ± 4% at day 10). The response was found similar to the one after an IA injection of Dexamethasone (79% ± 8% at day 7 and 81% ± 4% at day 10).*

(3) Liraglutide has analgesic properties and cartilage protection effects in collagenase-induced model in rats



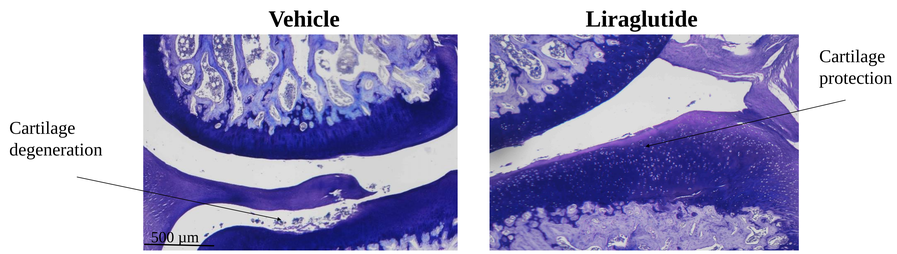


***Fig. 6:** In the rat collagenase OA model, two injections of type IV collagenase (500U in 25µl) were performed on days 1 and 4. Repeated IA injections of formulated Liraglutide or vehicle were performed once a week for 5 weeks. **A/** Liraglutide improved weight bearing deficit at multiple time-points (50% ± 4% at week 1, 66% ± 5% at week 3 and 66% ± 4% at week 6, p≤0.001) compared to vehicle (42% ± 4% at week 1, 57% ± 4% at week 3 and 59% ± 3% at week 6). **B/** Histological assessment of rat collagenase-injected right knee joint revealed a significant (p≤0.05) decrease of the total joint score in the IA Liraglutide treated group (8±4) compared to vehicle (11±4). **C/** Representatives pictures of right knee sections stained with toluidine blue showing that Liraglutide (right image) is able to mitigate focal extensive fibrillation and cartilaginous degeneration as compared to vehicle (left image), indicating cartilage protection.*

CONCLUSION

- **Anti-Inflammatory** — 1. Liraglutide treatment in *in vitro* OA model has shown significant decrease in the release of OA inflammatory and catabolic markers.
- **Analgesic** — 2. Intra-articular administration of formulated Liraglutide decreases pain in two animal models of OA.
- **Cartilage Protection** — 3. Intra-articular administration of formulated Liraglutide protects the joint from OA-related cartilage degradation.

Intra-articular administration of formulated liraglutide reduces pain, inflammation and cartilage degradation in in vitro and animal models of OA, opening the way to considering this drug as a potential disease-modifying OA drug (DMOAD).

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