Intra-articular Administration of Liraglutide Mitigates Synovial Tissue Alteration and Cartilage Degradation in Preclinical Osteoarthritis Models

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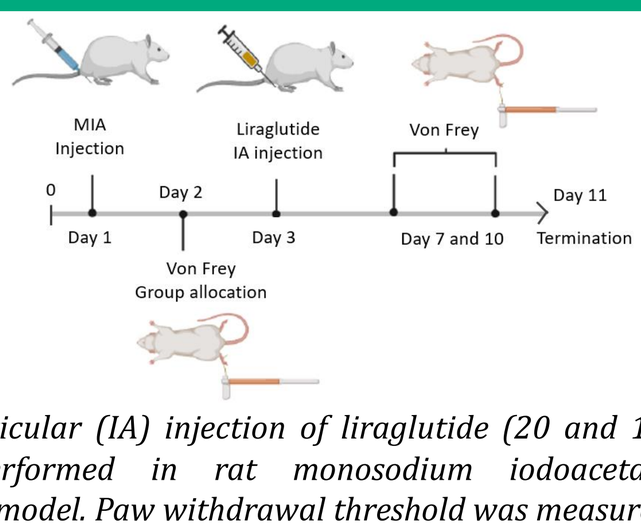
INTRODUCTION

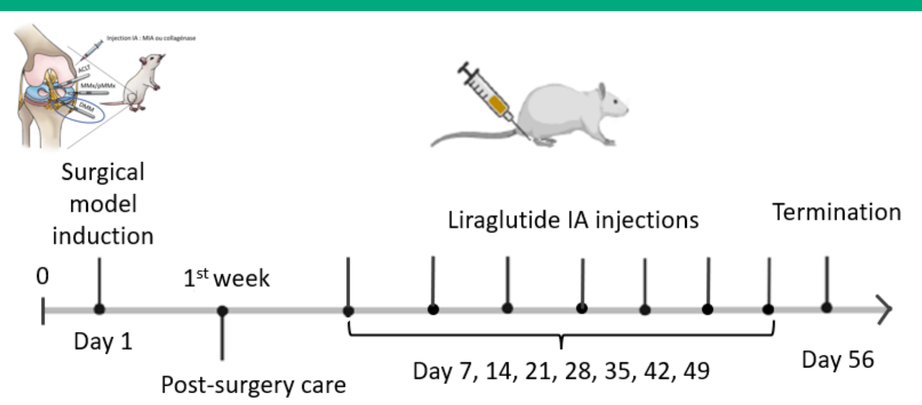
Despite its societal and economic impact, there's a lack of treatments able to act on the natural history of osteoarthritis (OA), urging the exploration of innovative strategies. Our team is focusing on glucagon-like peptide-1 (GLP-1) analogues, which have potential anti-inflammatory and tissue-protective effects beyond their antidiabetic properties. In this study, we aimed to explore the anti-inflammatory, anti-catabolic and anabolic effects of liraglutide, a GLP-1 analogue, in two *in vivo* models of OA by evaluating structural changes and surrogate markers of catabolism and anabolism in synovial membrane and cartilage in rats.

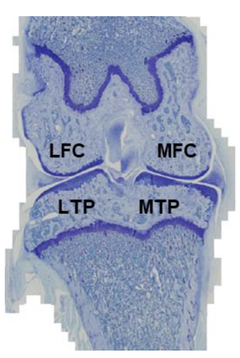
MATERIAL AND METHODS

Monoiodoacetate (MIA) model



Destabilization of the medial meniscus (DMM) model





LFC/MFC = lateral or medial femoral condyle
LTP/MTP = lateral of medial tibial plateau

Fig. 1: *Intra-articular (IA) injection of liraglutide (20 and 180 µg) or vehicle was performed in rat monosodium iodoacetate (MIA) inflammatory OA model. Paw withdrawal threshold was measured for pain behavior assessment at day 7 and 10. At the end of study, RT-qPCR or histopathological analyses were conducted blindly by two observers for evaluating synovial score (inner layer, density and inflammatory infiltrate, Krenn et al, 2006). The correlation curve between paw withdrawal threshold and synovitis score was calculated at day 10.*

Fig. 2: *Intra-articular (IA) injections of liraglutide (60 µg) or vehicle were performed once a week during 7 weeks in rat destabilization of the medial meniscus (DMM) surgically-induced OA model. At the end of study, histopathological analyses were conducted blindly by two independent investigators for evaluating OARSI score (from 0 to 26 in each quadrant, Pritzker et al, 2006) and osteophytes score (Gerwin et al, 2010) respectively.*

RESULTS

(1) Liraglutide decreases pain and synovitis in MIA rat inflammatory OA model

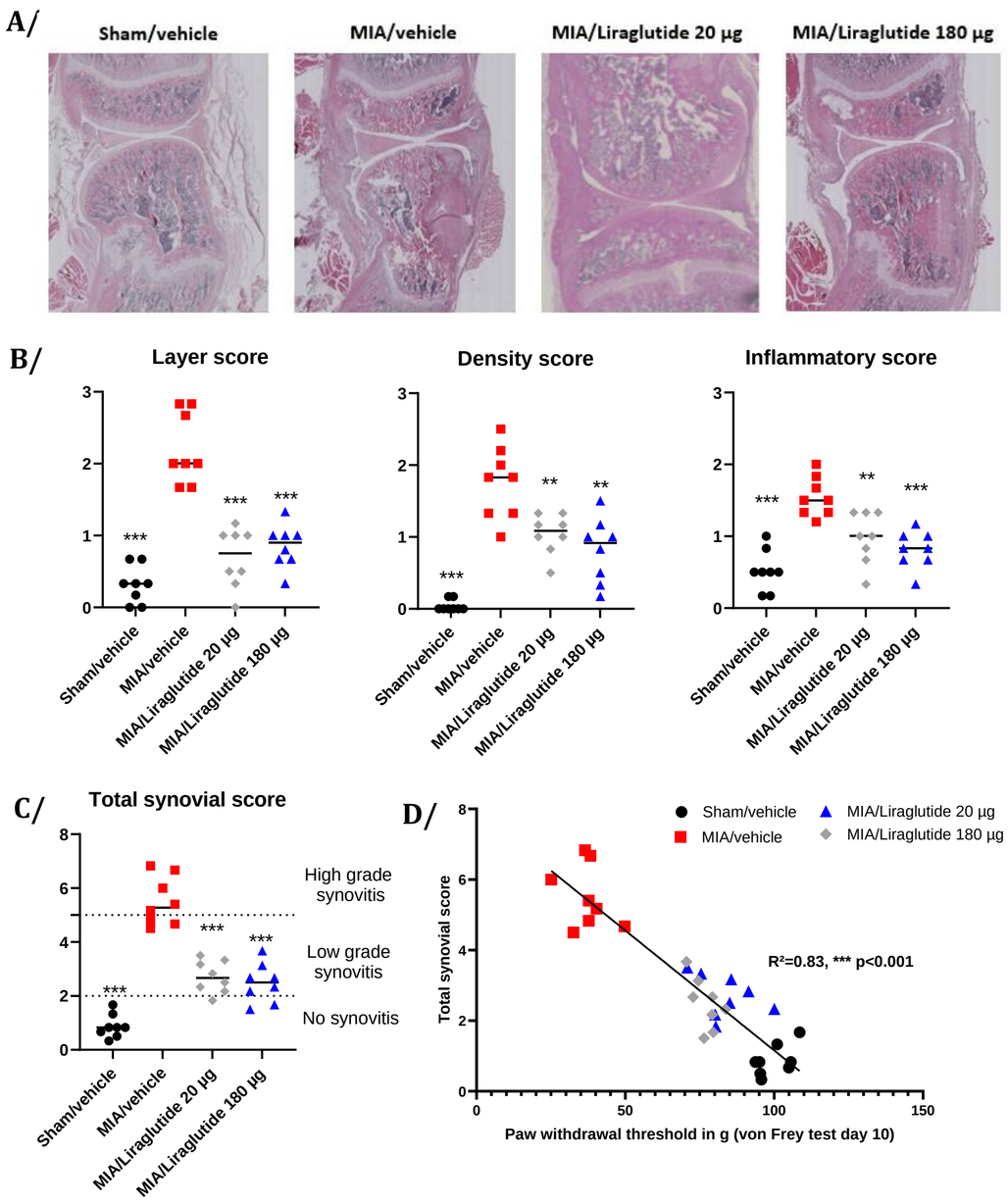
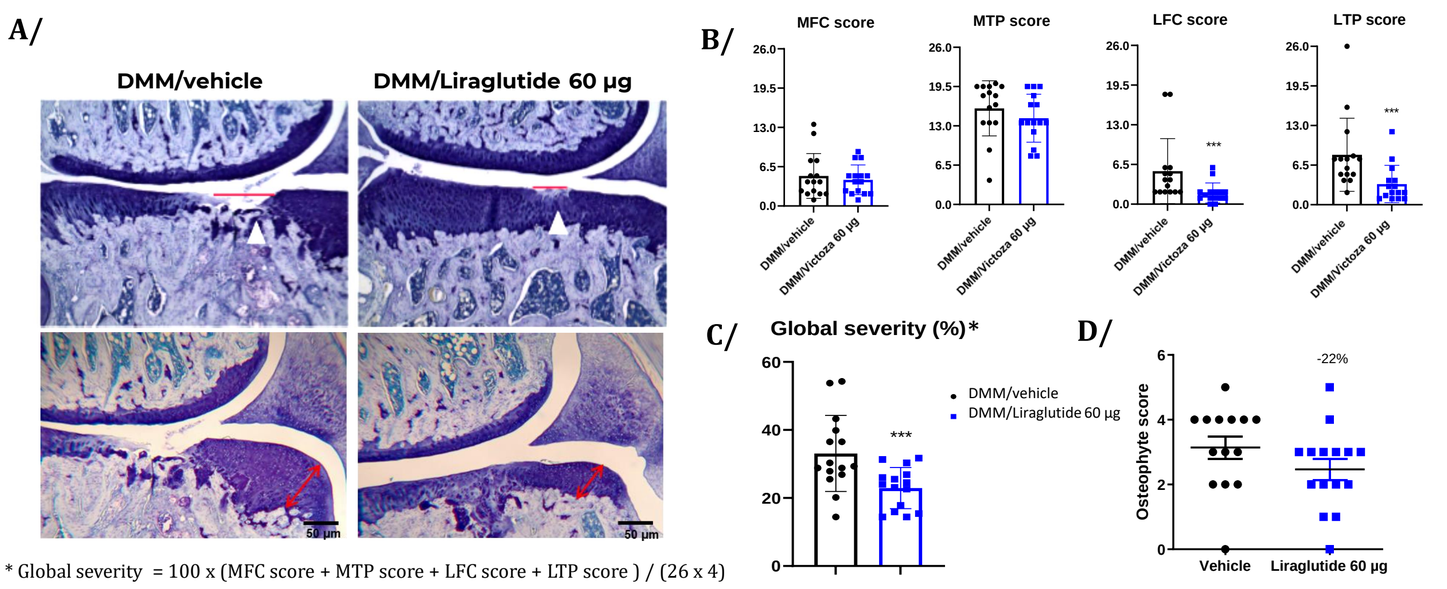


Fig. 3: *In a MIA rat model (n=8/group), a single injection of liraglutide is able to mitigate synovitis as compared to MIA/vehicle control group (p<0.001). **A/** Representative pictures of right knee sections stained with H&E. **B/** Liraglutide induces a significant and dose-dependent reduction of 3 parameters of the Krenn score: the inner layer (*** p<0.001), the density of resident cells (*** p<0.001 and **p<0.01) and inflammatory infiltrate (**p<0.01 for 20 µg and ***p<0.001 for 180 µg) in the synovial membrane compared to MIA/vehicle control group. **C/** Liraglutide treatment significantly reduces the total synovial structure score (p<0.001) in MIA rat model. **D/** Correlation analysis between synovitis score and the results of the von Frey test at day 10 indicates 83% of correlation (R^2= 0.83, p<0.001) between the total synovial score and pain.*

(2) Liraglutide protects the cartilage and bone structure in DMM model in rats



* Global severity = 100 x (MFC score + MTP score + LFC score + LTP score) / (26 x 4)

Fig. 4: *In a rat DMM model (n=15/group) liraglutide (right) is able to mitigate cartilaginous degradation and osteophytes formation as compared to vehicle (left), indicating structural protection. **A/** Representative pictures of right knee sections stained with toluidine blue. **B/** Liraglutide reduces significantly (***p<0.001) OARSI score in lateral femoral condyle (LFC) and lateral tibial plateau (LTP) compared to DMM/vehicle group **C/** Overall, liraglutide reduces the global severity index (***p<0.001). **D/** Liraglutide-treated DMM rats show a numerically reduced osteophyte score.*

(3) Liraglutide decreases catabolic mediators and induces anabolic mediators in cartilage in the rat MIA model

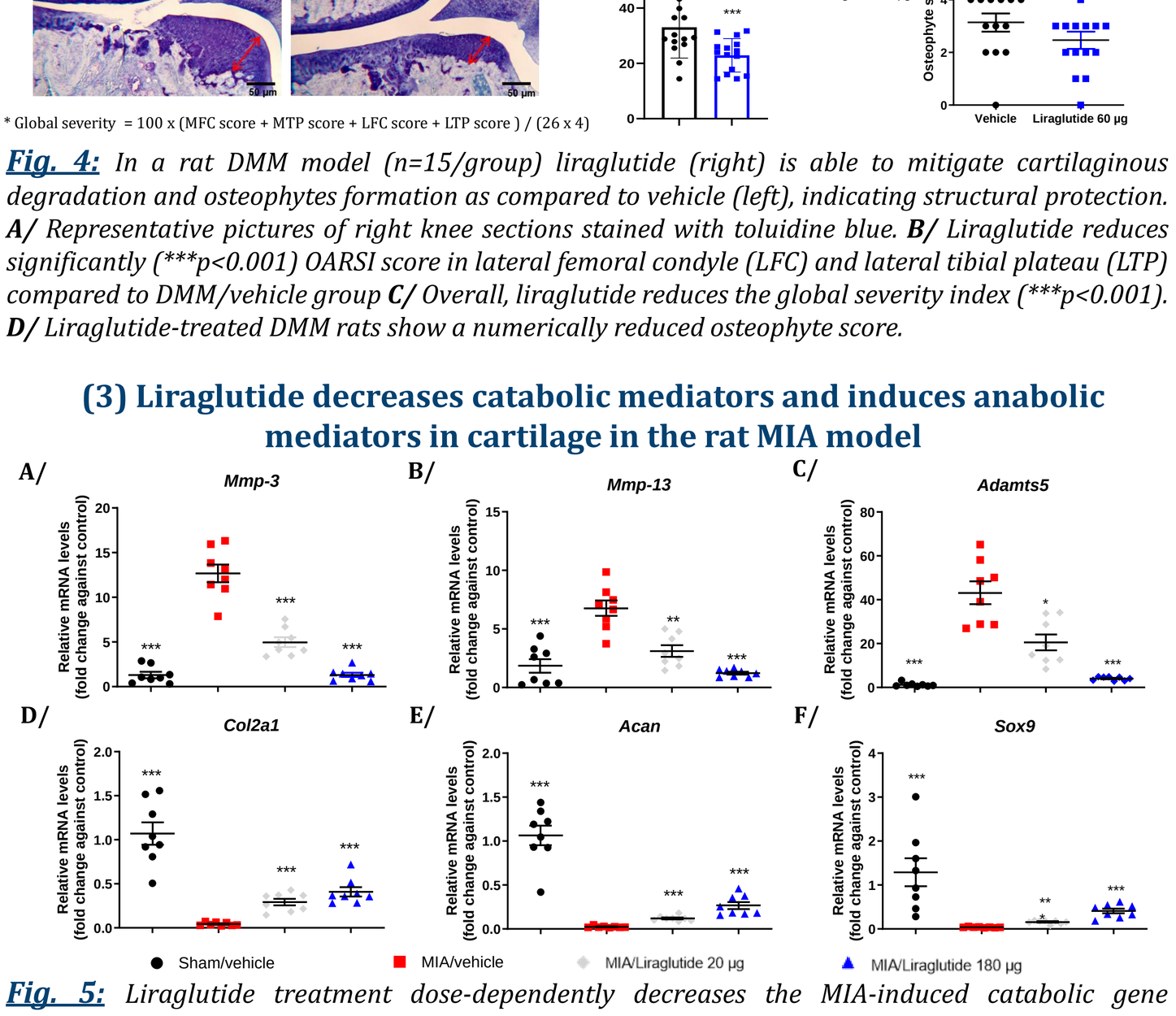


Fig. 5: *Liraglutide treatment dose-dependently decreases the MIA-induced catabolic gene expression of **A/** Mmp-3, **B/** Mmp-13 and **C/** Adamts5. MIA decreases gene expression of **D/** Col2a1, **E/** Acan and **F/** Sox9 anabolic markers, which are rescued in part by liraglutide in a dose-dependent manner (*p<0.05, **p<0.01 and ***p<0.001).*

CONCLUSION

1. Liraglutide has analgesic and protective effects on synovial membrane in the MIA rat model.
2. Liraglutide mitigates cartilage and bone degradation in the DMM rat model.
3. Liraglutide reduces catabolic and promotes anabolic mediators in cartilage in the MIA rat model.

These results confirm that intra-articular liraglutide targets relevant structural changes throughout the joint structure, delaying the natural history of the disease.

REFERENCES

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