Conclusions: In this nested case-control study, warfarin use, a vitamin K antagonist, was associated with significantly greater risk of KR (an indicator for end-stage knee OA) than DOAC use. This data adds further support to the importance of adequate vitamin K and vitamin K-dependent proteins for preventing and/or limiting progression of OA.

Table: Relation of Warfarin versus DOAC use to Risk of Knee Replacement

	KR cases	Controls
Subjects (n)	553	2226
Warfarin use	392 (70.9%)	1357 (61.0%)
Direct oral anticoagulant (DOAC) use	161 (29.1%)	869 (39.0%)
Odds Ratio (95% CI), matched for age & gender	1.78 (1.41, 2.24)	
Adjusted* Odds Ratio (95% CI), matched for age & gender	1.61 (1.26, 2.06)	

*adjusted for BMI, comorbidities (cancer, congestive heart failure, COPD, dementia, diabetes, hyperlipidemia, hypertension, ischemic heart disease, renal disease, stroke, venous thromboembolism/pulmonary embolus), medications (anti-hypertensives, insulin, oral anti-diabetic drugs, lipid-lowering drugs, NSAIDs, acetaminophen), general practitioner visits, hospitalizations

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PROTECTIVE EFFECTS OF INTRA-ARTICULAR FORMULATED LIRAGLUTIDE IN OSTEOARTHRITIS : PRECLINICAL STUDIES

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Purpose: 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. 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. The objective of this study was to evaluate the effects of intra-articular (IA) Liraglutide in *in vitro* and *in vivo* models of OA by evaluating surrogate markers of inflammation and cartilage matrix proteolysis, cartilage degradation and pain.
Methods: IL-1β-stimulated mouse articular chondrocytes were treated with different concentrations of Liraglutide for 24h. Production of matrix metalloproteinases (MMP) and prostaglandin E2 (PGE2) was measured by ELISA. IA injections of Liraglutide or vehicle were performed in two chemically-induced inflammatory knee OA models: the mouse monosodium iodoacetate (MIA) model and the rat collagenase model. 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: Liraglutide significantly reduced the IL-1β-induced production of PGE2 (1341±86 vs 1766±145 pg/ml for vehicle, $p \leq 0.05$, 50nM dose) and cartilage matrix catabolic enzymes MMP-3 (294±23 for vehicle vs 204±15 ng/ml, $p \leq 0.01$, 3nM dose; vs 197±23 ng/ml, $p \leq 0.001$, 50nM dose) and MMP-13 with a dose response (127±14 for vehicle vs 90±18 pg/ml, $p \leq 0.01$, 3nM dose; vs 70±10 ng/ml, $p \leq 0.001$, 10nM dose; vs 52±6 ng/ml, $p \leq 0.001$, 50nM dose) in murine chondrocytes. In both *in vivo* OA models, Liraglutide IA injections significantly attenuated pain symptoms. Indeed, in the mouse MIA model, single injection of IA Liraglutide increased paw withdrawal threshold (0.37±0.39 vs 0.13±0.11 g for vehicle, $p \leq 0.05$, day 7) and improved weight distribution to the affected limb (80±7% at day 7 and 83±4% at day 10, $p \leq 0.001$) 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). In the rat collagenase OA model, repeated IA injections of 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, $p \leq 0.001$) compared to vehicle (42±4 at week 1, 57±4 at week 3 and 59±3% at week 6). Histological assessment of rat collagenase-injected knee joint revealed a significant ($p \leq 0.05$) decrease of the total joint score in the IA Liraglutide treated group (8±4) compared to vehicle (11±4).
Conclusions: IA injection of Liraglutide has demonstrated anti-catabolic, anti-inflammatory and pain-relieving effects in preclinical OA models, opening the wave to considering now this molecule as a potential disease-modifying OA drug.

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INTRAARTICULAR INJECTION OF MM-II LIPOSOMES LUBRICATES CARTILAGE IN-VIVO AND REDUCES FRICTION AND WEAR IN EX-VIVO CARTILAGE MODELS

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Purpose: MM-II is a suspension of large multilamellar liposomes for intra-articular administration, under development for treatment of osteoarthritic pain. Due to their unique characteristics, MM-II liposomes are retained on the cartilage surface, providing long-term lubrication and leading to a reduction in wear of the cartilage. As previously reported in a first-in-human clinical trial, MM-II, when injected intraarticularly, was shown to reduce pain up to 3 months post injection. This study aims to illustrate MM-II's mechanism of action by studying the localization of the liposomes in the joint following an intraarticular injection into rabbits and using 2 *ex-vivo* cartilage models for evaluation of MM-II's lubrication capabilities and its effect on reduction of friction and wear of the cartilage.
Methods: Three different studies were conducted for the evaluation of MM-II's localization in the knee post injection and its effect on reduction of cartilage wear and friction. MM-II knee localization after intra-articular injection into rabbits: Tritium-labeled MM-II liposomes were injected into the knee joint of New Zealand white rabbits. Analysis of the biodistribution of radioactivity in the knee joint was performed at selected time points following administration. Imaging of the distribution of radioactivity in the knee joint was undertaken using quantitative whole-body autoradiography (QWBA) and micro-autoradiography (MARG) techniques. *Ex-vivo* friction measurement: Friction measurement was conducted using a cartilage-on-cartilage rotation friction test setup, using a pair of osteochondral equine cores (12 mm bottom core and 7.8 mm upper core) immersed in a bath containing the tested lubricant maintained at 37°C. Friction measurement was performed using a mechanical tester equipped with a multiple-axis load cell. Static and kinetic friction coefficients obtained using MM-II as a lubricant were compared with healthy synovial fluid (positive control) and phosphate buffered saline (negative control). *Ex-vivo* wear measurement: Wear tests were carried out using a pin-on-disc setup with porcine cartilage pins sliding against Cobalt-Chromium-Molybdenum (CoCrMo) discs immersed in a bath containing the tested lubricant maintained at 37°C. Wear assessement was performed by measurement of cartilage pin height and weight before and after application of wear cycles under a predetermined load. The effect of MM-II on wear of the cartilage pin was evaluated against a protein-based lubricant commonly used for wear testing of prostheses.
Results: Distribution of radioactivity following intraarticular injection of MM-II into rabbit knee showed high concentrations of radioactivity in the articular space after injection. Seven days post injection, radioactivity concentration was found to be reduced in the synovial cavity and a high radioactivity concentration was observed on the cartilage, implying that MM-II is selectively bound to the surfaces of the cartilage. Radioactivity was detected on the cartilage surface for up to 56 days post injection. Evaluation of the friction coefficient was performed at a static phase and kinetic phase. For the static friction coefficients, MM-II presented a statistically significant lower coefficient when compared to Phosphate Buffered Saline (0.11versus 0.16, respectively; $p<0.0001$) or to synovial fluid (0.11versus 0.15, respectively; $p=0.05$). For Kinetic friction coefficient, MM-II showed a statistically significant lower coefficient than Phosphate Buffered Saline (0.028 versus 0.035, respectively; $p=0.008$), but statistically higher than synovial fluid (0.028 versus 0.022, respectively; $p=0.002$). As for assessment of the effect of MM-II on cartilage wear, MM-II was shown to reduce the mass and height loss when compared to protein-based liquid (14 mg versus 39 mg mass decrease, respectively, and 0.5 mm versus 1.2 mm length decrease, respectively; $p=0.05$).
Conclusions: Our data illustrates the role that MM-II liposomes can play in lubrication of the knee joint. Due to their unique characteristics, after intraarticular injection MM-II liposomes adsorb to the cartilage surface and provide lubrication for movement between the cartilage