Nouveaux Anti-diabétiques oraux : pourquoi le rhumatologue doit s'y intéresser ?

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Cas clinique 1

Mme Priscillia R; 43 ans

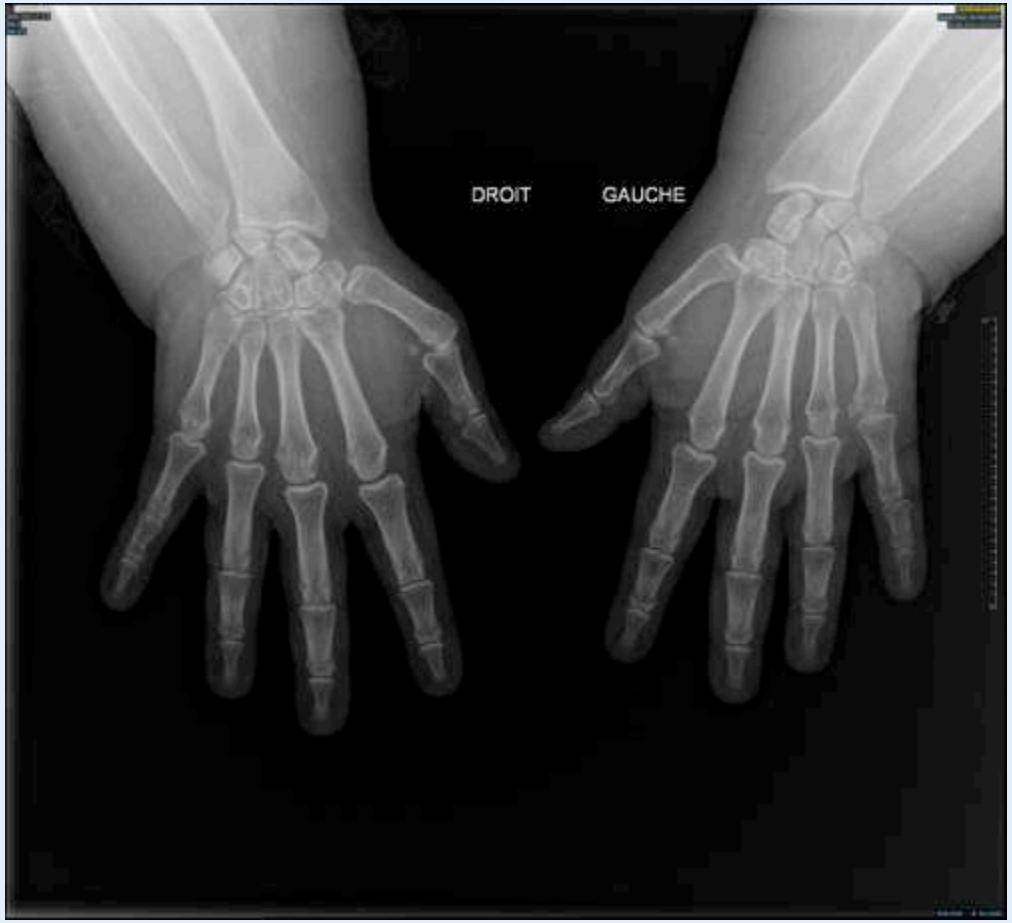
Obésité grade 3 : 168kg , 147cm, tour de taille 158cm

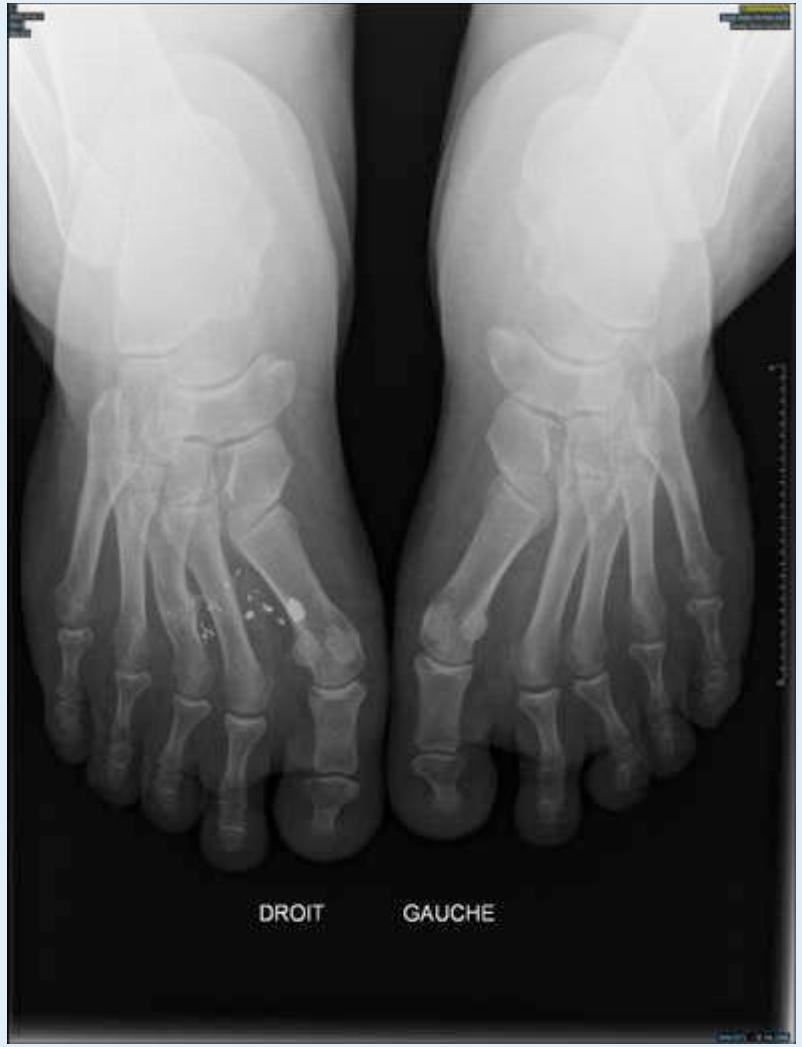
Complications:

- **Dyslipidémie**
- **SAOS appareillé**
- **Diabète type 2**
- **Échec de 3 chirurgies bariatriques**

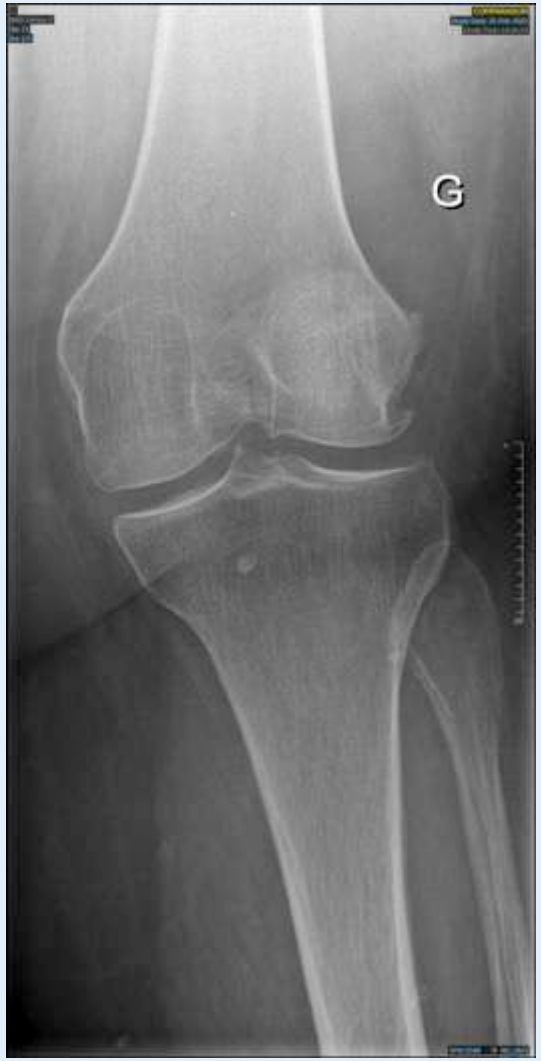
Suivi pour PR CCP+ sous TOCILIZUMAB

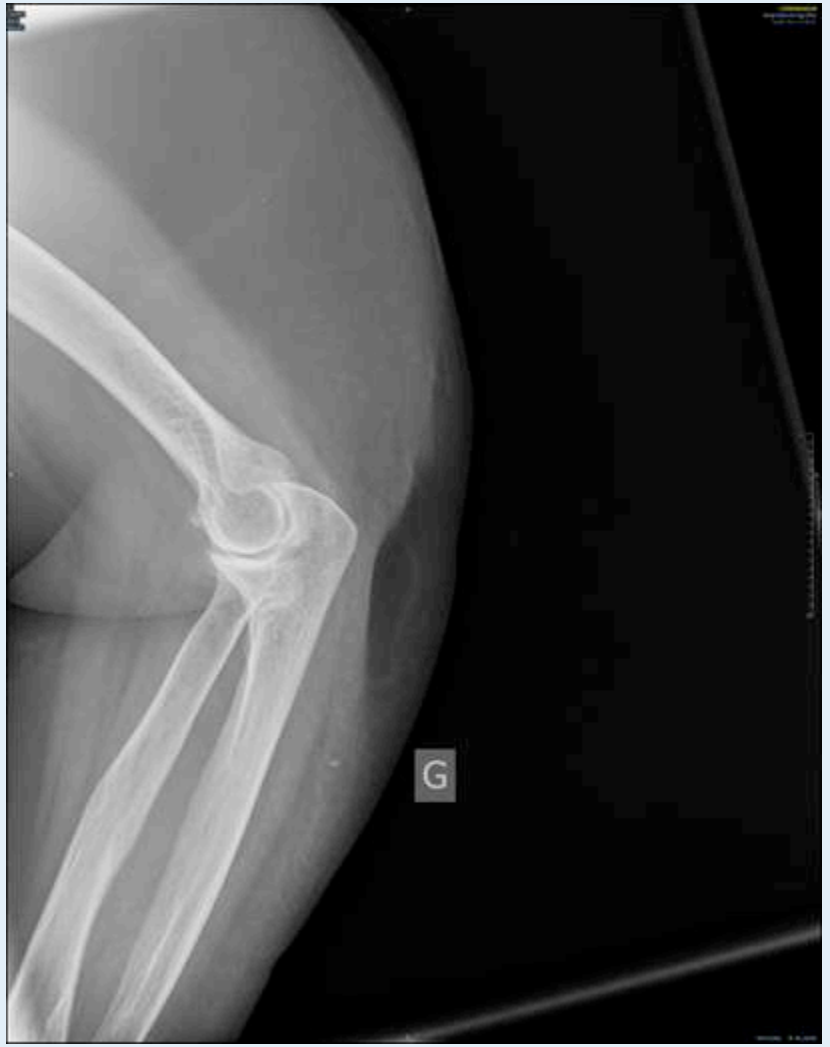
Cas clinique 1





Cas clinique 1





Cas clinique 1

Traitement actuel

- STAGID
- LEVOTHYROX
- VOLTARENE (si besoin)
- OGASTORO
- TAHOR

Cas clinique 1

Indication opératoire sur coudes

AP limitée par les gonalgies

Contexte DT2 + HbA1c 7% + Obésité morbide

Cas clinique 1

Lesquels des traitements antidiabétiques suivants entrainent une réduction pondérale ?

1. **Insuline**
2. **Sulfamides hypoglycémiant**
3. **Analogues GLP-1**
4. **Inhibiteurs SGLT-2**
5. **Inhibiteurs DPP4**

Cas clinique 1

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Analogues GLP-1 et arthrose

Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial

Henrik Gudbergsen,[1] Anders Overgaard,[1] Marius Henriksen,[1,2] Eva Ejlersen Wæhrens,[1,3] Henning Bliddal,[1] Robin Christensen,[1,4] Sabrina Mai Nielsen,[1,4] Mikael Boesen,[1,5] Filip Krag Knop,[6,7] Arne Astrup,[8] Marianne Uggen Rasmussen,[1] Cecilie Bartholdy,[1,2] Cecilie Laubjerg Daugaard,[1] Karen Ellegaard,[1] Berit Lilienthal Heitmann,[9,10] Else Marie Bartels,[1,11] Bente Danneskiold-Samsøe,[1] and Lars Erik Kristensen[1]

Gudbergsen H et al. Am J Clin Nutr 2021;113:314–323

Analogues GLP-1 et arthrose

- Intervention diététique (semaine -8 à 0)
- À la semaine 0, les patients ayant perdu >5% de leur poids corporel ont été randomisé en 2 bras : liraglutide 30 mg/j ou placebo pendant 52 semaines.
- CJP : co-critère poids + sous-échelle douleur du KOOS

Gudbergsen H et al. Am J Clin Nutr 2021;113:314–323

Analogues GLP-1 et arthrose

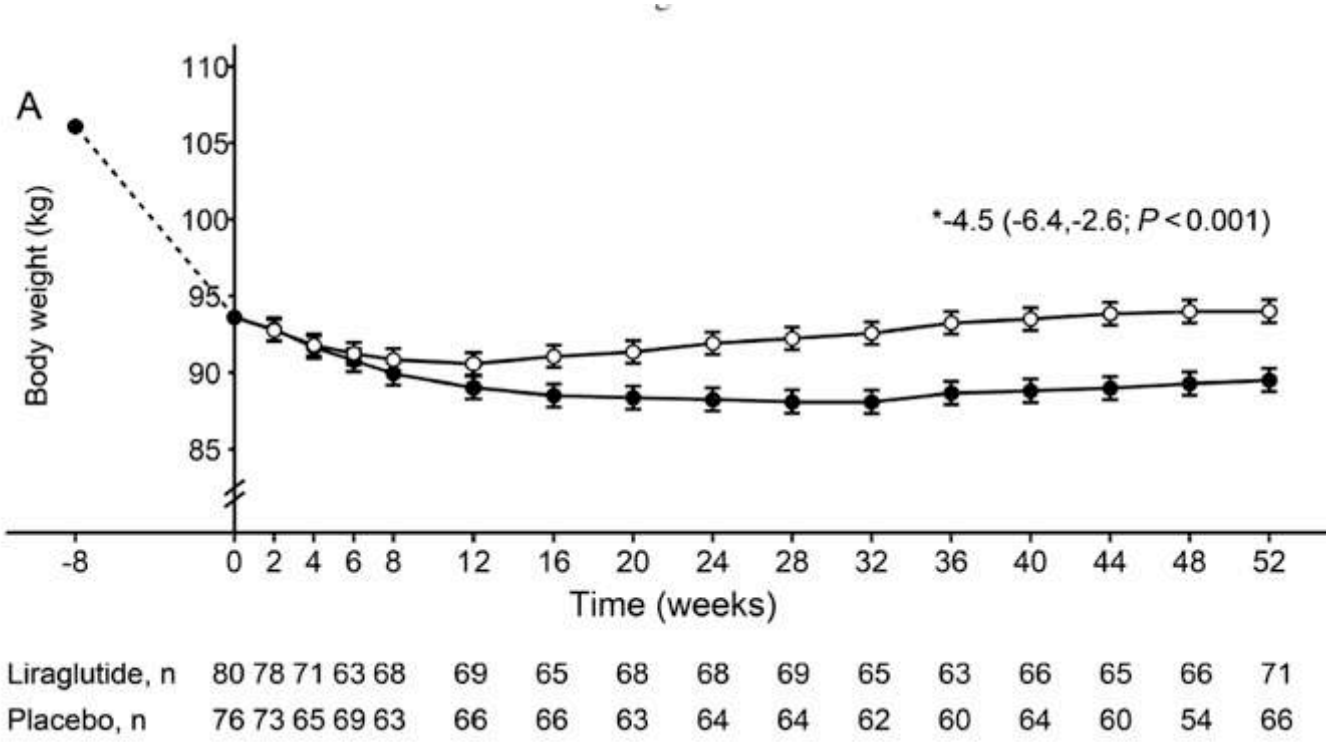
TABLE 1 Baseline characteristics of all randomly assigned participants (the ITT population)[1]

Characteristic	Total ($n = 156$)	Liraglutide ($n = 80$)	Placebo ($n = 76$)
Female sex, *n* (%)	101 (65%)	52 (65%)	49 (64%)
Age, y	59.2 ± 10.3	59.2 ± 10.8	59.3 ± 9.7
Height, m	170.6 ± 8.8	171.2 ± 8.1	170.0 ± 9.6
Kellgren Lawrence score, *n* (%)			
Kellgren Lawrence score 1	23 (14.9%)	10 (12.4%)	13 (17.1%)
Kellgren Lawrence score 2	68 (43.6%)	35 (43.8%)	33 (43.4%)
Kellgren Lawrence score 3	65 (41.7%)	35 (43.8%)	30 (39.5%)
Weight, kg	93.6 ± 16.6	96.3 ± 18.2	90.8 ± 14.3
Change in weight from enrollment, kg	–12.5 ± 3.8	–12.8 ± 4.0[4]	–12.1 ± 3.6[4]
BMI	32.1 ± 4.9	32.8 ± 5.5	31.3 ± 4.0
Waist circumference, cm	103.7 ± 12.7	105.5 ± 13.9	101.8 ± 11.1
Hip circumference, cm	113.4 ± 11.1	115.2 ± 12.5	111.4 ± 9.1
KOOS score,[2] points			
Pain	77.8 (69.4–86.1)	76.4 (69.4–87.5)	77.8 (69.4–86.1)
Change in pain from enrollment	11.1 (2.8–19.4)	11.1 (2.8–19.4)[4]	11.1 (5.6–18.1)[4]
Symptoms	82.1 (67.9–89.3)	80.4 (67.9–89.3)	82.1 (67.9–89.3)
Function in activities of daily living	85.3 (73.5–92.6)	83.8 (71.3–91.2)	86.8 (76.5–94.1)
Knee-related quality of life	50.0 (37.5–62.5)	50.0 (37.5–56.3)	56.3 (37.5–68.8)
Function in sports and recreation	50.0 (30.0–75.0)	50.0 (30.0–67.5)	52.5 (30.0–75.0)
ICOAP questionnaire,[3] points			
Total score	15.9 (6.8–29.5)	15.9 (6.8–28.4)	18.2 (9.1–29.5)
Constant pain subscore	10.0 (0.0–25.0)	10.0 (0.0–25.0)	10.0 (0.0–25.0)
Intermittent pain subscore	25.0 (8.3–33.3)	20.8 (8.3–33.3)	25.0 (12.5–33.3)

Gudbergsen H et al. Am J Clin Nutr 2021;113:314–323

Analogues GLP-1 et arthrose

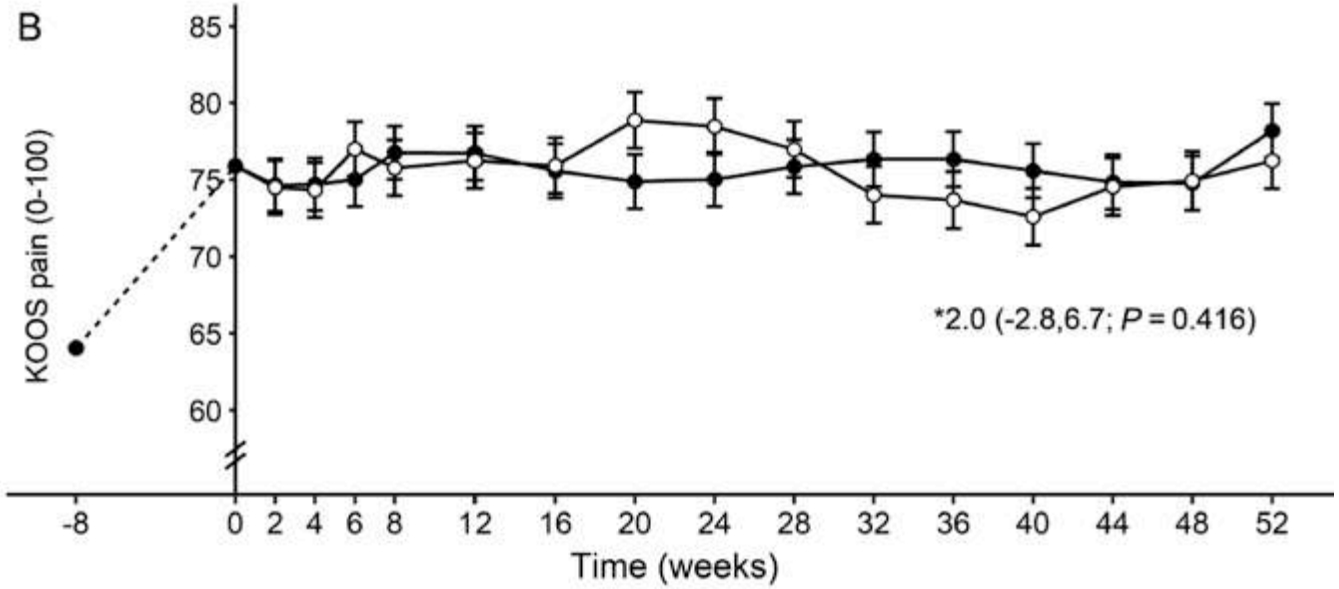
- Résultats:
  - **Différence significative du poids** poids en faveur du groupe liraglutide (variations moyennes : -2,8 et +1,2 kg; différence entre les groupes : 3,9 kg ; IC à 95 % : -6,9, -1,0 ; P = 0,008)



Gudbergsen H et al. Am J Clin Nutr 2021;113:314–323

Analogues GLP-1 et arthrose

- Résultats:
  - **Pas de différence entre les groupes sur la douleur KOOS** (changements moyens : 0,4 et -0,6 points, respectivement ; différence entre les groupes : 0,9 points ; IC à 95 % : -3,9, 5,7 ; P = 0,71)



Gudbergsen H et al. Am J Clin Nutr 2021;113:314–323

Analogues GLP-1 et arthrose

Osteoarthritis

OPEN ACCESS

CLINICAL SCIENCE

Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort

Hongyi Zhu ,[1,2] Lenian Zhou,[1,2] Qiuke Wang ,[3] Qianying Cai,[1,2] Fan Yang,[1] Hanqiang Jin,[1] Yiwei Chen,[1] Yanyan Song,[4] Changqing Zhang [1,2]

Hongyi Zhu et al; Ann Rheum Dis 2023

Analogues GLP-1 et arthrose

- Design:
  - étude de cohorte prospective de Shanghai
  - plus de 40 000 adultes âgés de plus de 45 ans souffrant d'arthrose
  - identifié tous les participants présentant une comorbidité de DT2 et recrutés entre le 1er janvier 2011 et le 1er janvier 2017
- CJP: incidence de la chirurgie du genou

Hongyi Zhu et al; Ann Rheum Dis 2023

Analogues GLP-1 et arthrose

- Résultats

Table 1 Baseline patient characteristics

	GLP-1RA (n=233)	Non-GLP-1RA (n=1574)
Age, years	60.7 (8.7)	61.2 (8.6)
Sex, No. (%)		
Male	59 (25.3%)	429 (27.3%)
Female	174 (74.7%)	1145 (72.7%)
Weight, kg	66.0 (12.2)	65.1 (12.3)
BMI, kg/m^2	25.2 (3.7)	25.1 (3.6)
HbA1c, %	7.3 (1.6)	7.2 (1.5)
Duration of diabetes, years	8.1 (6.0)	8.3 (5.8)
Duration since initial clinically diagnosed KOA, years	5.8 (5.8)	5.5 (5.8)
SBP (mmHg)	129.3 (16.2)	130.5 (16.4)
DBP (mmHg)	79.5 (10.9)	80.1 (11.3)
Current smoker, No. (%)	24 (10.3%)	173 (11.0%)
Use antidiabetes agents, No. (%)		
Oral antidiabetes drugs	218 (93.5%)	1454 (92.4%)
Insulin	148 (63.5%)	991 (63.0%)
Kellgren-Lawrence grade, No. (%)		
Grade I	30 (12.9%)	221 (14.0%)
Grade II	131 (56.2%)	875 (55.6%)
Grade III	72 (30.9%)	478 (30.4%)
Predominantly lateral KOA, No. (%)	42 (18.0%)	298 (18.9%)
WOMAC total score	19.3 (9.7)	19.8 (9.6)
WOMAC pain subscore	18.3 (13.8)	17.4 (12.3)
WOMAC stiffness subscore	18.2 (12.1)	18.3 (15.5)
WOMAC function subscore	19.7 (12.6)	20.7 (11.9)

Table 2 Comparison of treatment, PROs and incident knee surgery between GLP-1RA and non-GLP-1RA groups

	GLP-1RA (n=233)	Non-GLP-1RA (n=1574)	Adjusted mean difference* (95% CI)	P value	Adjusted P value*
Weight, kg					
At last follow-up	61.4 (14.0)	67.8 (13.6)	-	<0.001	-
Change from baseline	−4.60 (8.07)	2.69 (5.23)	−7.29 (−8.07, −6.50)	<0.001	<0.001
HbA1c, %					
At last follow-up	7.3 (1.5)	7.3 (1.6)	-	0.79	-
Change from baseline	0.02 (1.26)	0.08 (1.23)	−0.05 (−0.22, 0.12)	0.53	0.56
WOMAC total score					
At last follow-up	21.9 (10.3)	23.4 (10.0)	-	0.039	-
Change from baseline	2.65 (14.17)	3.58 (13.99)	−1.46 (−2.84, −0.08)	0.35	0.038
WOMAC pain subscore					
At last follow-up	17.1 (12.6)	19.4 (12.5)	-	0.010	-
Change from baseline	−1.18 (19.00)	2.01 (17.60)	−3.37 (−5.79, −0.94)	0.011	0.007
WOMAC stiffness subscore					
At last follow-up	24.0 (15.8)	24.7 (15.8)	-	0.54	-
Change from baseline	5.79 (21.08)	6.33 (20.43)	−1.05 (−3.35, 1.25)	0.71	0.37
WOMAC function subscore					
At last follow-up	23.1 (12.3)	24.4 (12.3)	-	0.13	-
Change from baseline	3.41 (17.65)	3.72 (17.25)	−0.95 (−2.71, 0.81)	0.80	0.29
Annual consumption of oral NSAIDs and acetaminophen, RDD/year	15.2 (13.8)	16.9 (14.5)	−1.63 (−3.62, 0.36)	0.10	0.11
Annual consumption of topical NSAIDs, RDD/year	21.7 (22.7)	23.6 (22.8)	−1.92 (−5.06, 1.21)	0.22	0.23
Annual consumption of opioids, MME/year	109.0 (190.0)	126.2 (205.6)	−17.07 (−45.09, 10.94)	0.20	0.23
Total no of intra-articular therapies	7.5 (13.4)	9.7 (15.3)	-	0.022	-
Annual no of intra-articular therapies, per year	1.07 (1.99)	1.30 (2.12)	−0.24 (−0.53, 0.05)	0.10	0.10
Annual no of intra-articular injection of steroids, per year	0.13 (0.28)	0.22 (0.39)	−0.087 (−0.14, − 0.036)	<0.001	0.001
Follow-up, years	7.7 (1.5)	7.8 (1.6)	-	0.71	-
Knee surgery	4 (1.7%)	93 (5.9%)	-	0.005	0.014

Hongyi Zhu et al; Ann Rheum Dis 2023

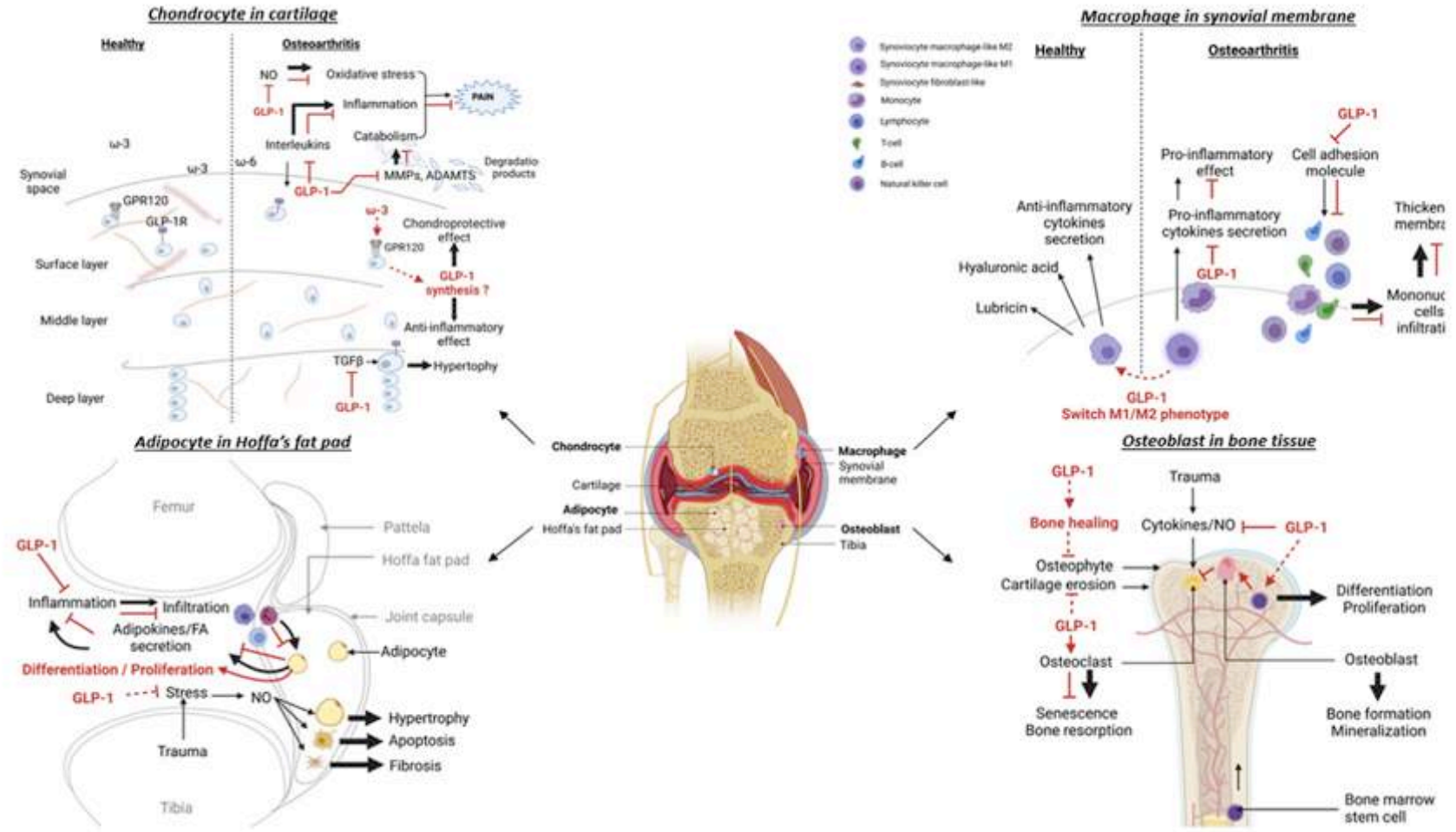
Analogues GLP-1 et arthrose

- Conclusions
  - L'association entre l'exposition au GLP-1RA et la diminution de l'incidence de la chirurgie du genou a été **médiée par la réduction du poids** (proportion de médiation : 32,1%), plutôt que par le contrôle de la glycémie (trop faible pour être calculée)
  - **Manque de données, imputations multiples, suivi IRM imparfait, DT2 seulement mais biais d'indications, nbx switch TT durant le suivi…**

Hongyi Zhu et al; Ann Rheum Dis 2023

Analogues GLP-1

Perspectives en rhumatologie ?



Meurot C. J Orthopaedic Translation 2022

scientific reports

OPEN

Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis

C. Meurot[1], C. Martin[1], L. Sudre[1], J. Breton[1], C. Bougault[2], R. Rattenbach[1,3], K. Bismuth[1], C. Jacques[2] & F. Berenbaum[3,4]✉

Méthodologie

- 6 patients OA pour arthroplastie
- Modèle OA de souris MIA (Sodium monoiodoacetate)
  - Inhibits GA3PDH (Krebs cycle)
  - Chondrocyte deaths
  - Rapid inflammation and pain in 7 days
  - Histologic lesions can be seen as soon as 1 to 3 days post-MIA
  - Pain behaviour +++
  - Mice and rats

Serra CI. Vet Clin Exot Anim 2019

Résultats

- GLP-1R est exprimé dans le cartilage et la synoviale des tissus humains OA et des tissus articulaires non-OA de souris

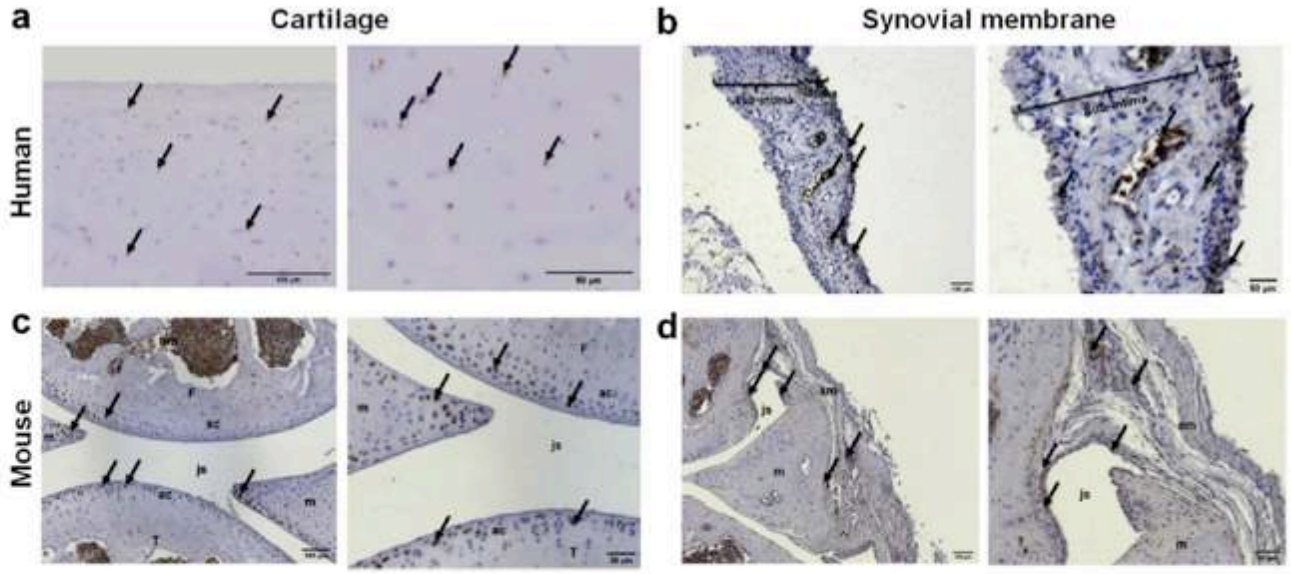


Figure 1. Expression of GLP-1 receptor in OA human and non-OA mouse knee joint. (**a**) Immunohistochemical staining of human OA knee cartilage sections was performed to determine the presence of GLP-1R (Mankin score: 3/14, scale bar = 100 µm or 50 µm). (**b**) Immunohistochemical staining of human OA synovial membrane sections was performed to determine the presence of GLP-1R (*si:* subintima, *i:* intima, *v:* blood vessel, scale bar = 100 µm or 50 µm). (**c**) Immunohistochemical staining of non-OA mice knee joint sagittal sections to determine the presence of GLP-1R (*ac:* articular cartilage, *m:* meniscus, *js:* joint space, *T:* tibia, *F:* femur, *bm:* bone marrow, scale bar = 100 µm or 50 µm). (**d**) Immunohistochemical staining of non-OA mice synovial membrane sagittal sections to determine the presence of GLP-1R (*sm:* synovial membrane, *js:* joint section, *m:* meniscus, scale bar = 100 µm or 50 µm). Control experiment was performed without primary antibody incubation. Arrows indicate example of cells positive for GLP-1R staining.

Résultats

- Le liraglutide en IA atténue le comportement lié à la douleur dans un modèle de souris arthrosique au MIA (court / long terme +++)

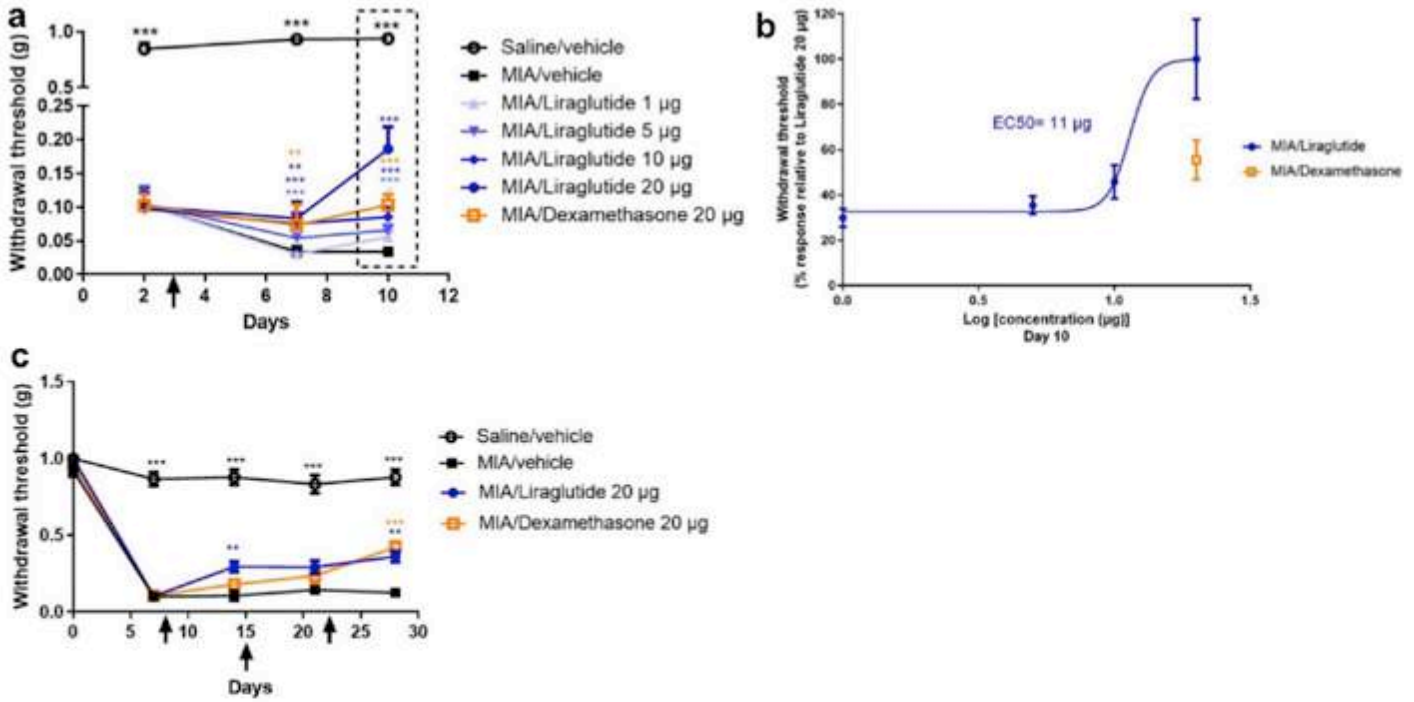


Figure 2. Liraglutide displayed analgesic effect in MIA mice models of OA. Mice knee joints were intra-articularly (IA) injected with 0.75 mg of MIA or saline on day 1. For the short-term study (**a**,**b**), treatments (liraglutide, dexamethasone, or vehicle) were injected IA on day 3 and inflammation pain sensitivity was determined by the von Frey test on day 2 (for randomization), 7, and 10 (n = 15–19 per group). For the long-term study (**c**), treatments were administered on days 8, 15, and 22, and von Frey tests were performed on day 7 (for randomization), 14, 21, and 28 (n = 9–10 per group). (**a**) Paw withdrawal threshold was assessed by von Frey filament stimulation on days 2, 7, and 10. (**b**) The efficacy rate of liraglutide in the MIA short-term study was

Résultats

- Cet effet analgésique semble lié à l'action anti-inflammatoire du liraglutide, avec une amélioration du score de sévérité de la synovite

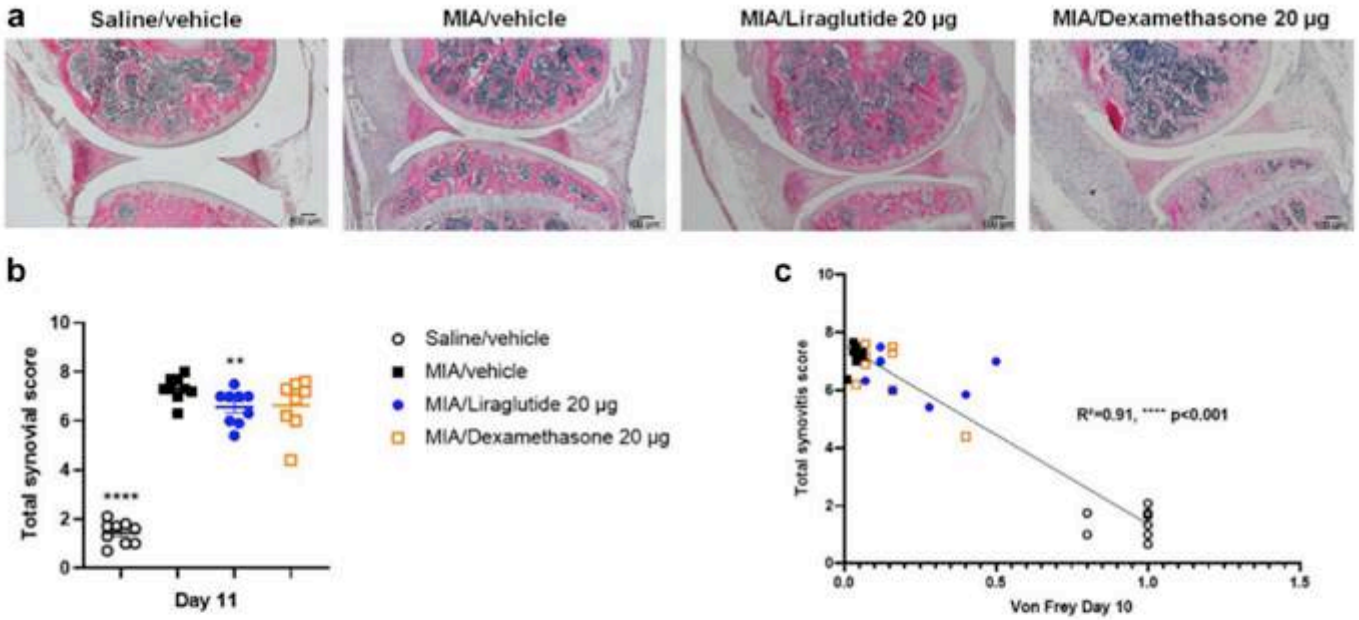


Figure 3. Liraglutide displayed anti-inflammatory effect in vivo in short-term MIA mice model of OA. Mice knee joints were intra-articularly (IA) injected with 0.75 mg of MIA or saline on day 1. Treatments (liraglutide, dexamethasone, or vehicle) were IA injected on day 3 (n = 15–19 per group). At the end of the study, on day 11, the mice were euthanized, and the right knee joint was recovered for histological analyses. (**a**) Representative photographs of sagittal sections of the paws of mice IA injected with 0.75 mg of MIA to induce inflammation and subsequently IA treated with vehicle, liraglutide or dexamethasone (positive control). (**b**) Histogram representing the total synovitis score calculated from Krenn et al., synovitis score system (n = 8–9 per group). (**c**) Based on the results of the von Frey test on day 10 and the synovitis score obtained for each animal, a correlation curve between these two parameters was calculated using GraphPad Prism 9.0 (n = 8–9 per group). Statistical analysis: Mean ± SEM. Mann–Whitney test with sequential strategy, $^{**}p < 0.01$, $^{****}p < 0.0001$ versus MIA control. Simple linear regression, $^{****}p < 0.0001$.

Résultats

- GLP-1R est la cible principale du liraglutide dans les chondrocytes et les macrophages
- L'effet anti-inflammatoire du liraglutide est médié par le récepteur GLP-1
- GLP-1R antagonist, exendin 9–39

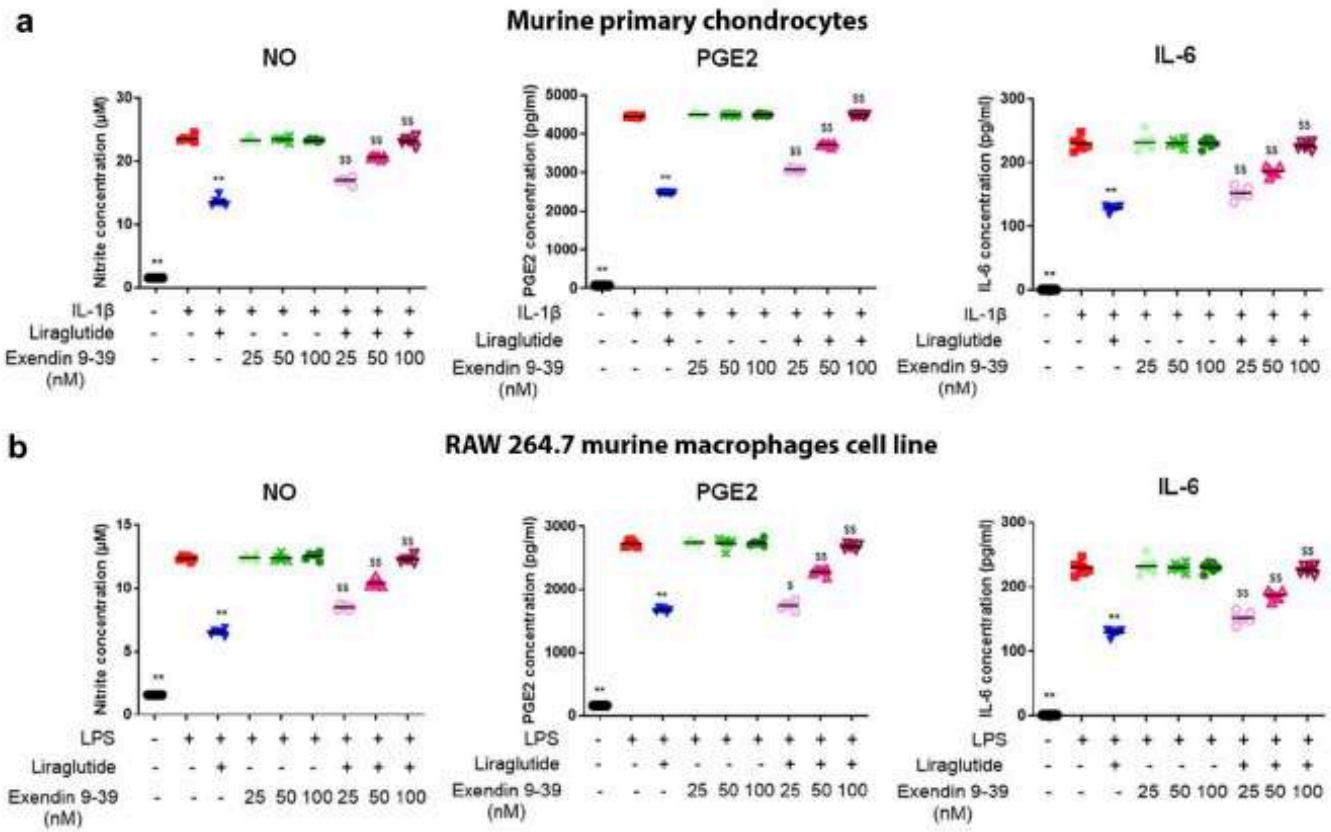
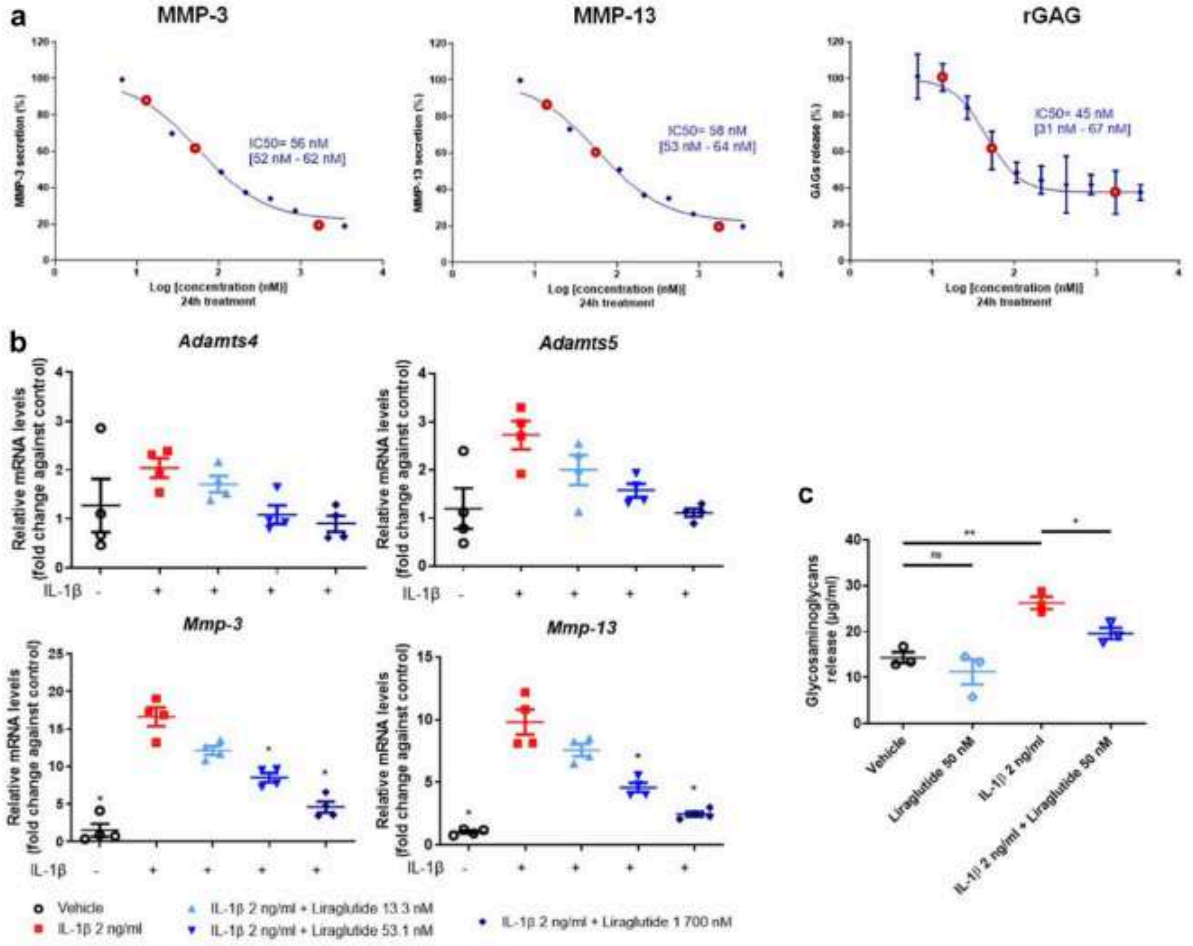


Figure 6. Anti-inflammatory effects of liraglutide are mediated by the GLP-1 receptor pathway. Primary cultured murine articular chondrocytes were incubated with 2 ng/mL IL-1β (**a**) and RAW 264.7, which were incubated with 100 ng/mL LPS (**b**) and co-treated with 50 nM of liraglutide or co-treated with three doses of exendin fragment 9–39 (25 nM, 50 nM, and 100 nM) for 24 h (n = 6). Nitrite, PGE_2, and IL-6 concentration of the supernatant was determined. Statistical analysis: Mean ± SEM, Mann–Whitney test with sequential strategy, $^{**}p < 0.01$, versus stimulated control (IL-1β or LPS) and $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, versus IL-1β + liraglutide or LPS + liraglutide group.

Résultats

- Le liraglutide peut atténuer la dégradation du cartilage par un effet anti-catabolique sur MMP/ADAMTS (produits par chondrocytes primaires)
- NB: **IL-1b stim**



Conclusions

- Effets pléiotropes DMOAD ?
- Essai en cours et/ou à mener
- Preuve de concept +++

- 1 seul modèle mais autre publication avec un autre modèle chirurgical + (stress RE, apoptose, inflammation)
- Pas de critère structural (uCT)
- Pas de datas sur os sous-chondral
- Cohorte obèse : pas d'effets ?

Cas clinique 2

Mme Fatma B, 76 ans

PR sous corticothérapie 5mg + ETANERCEPT

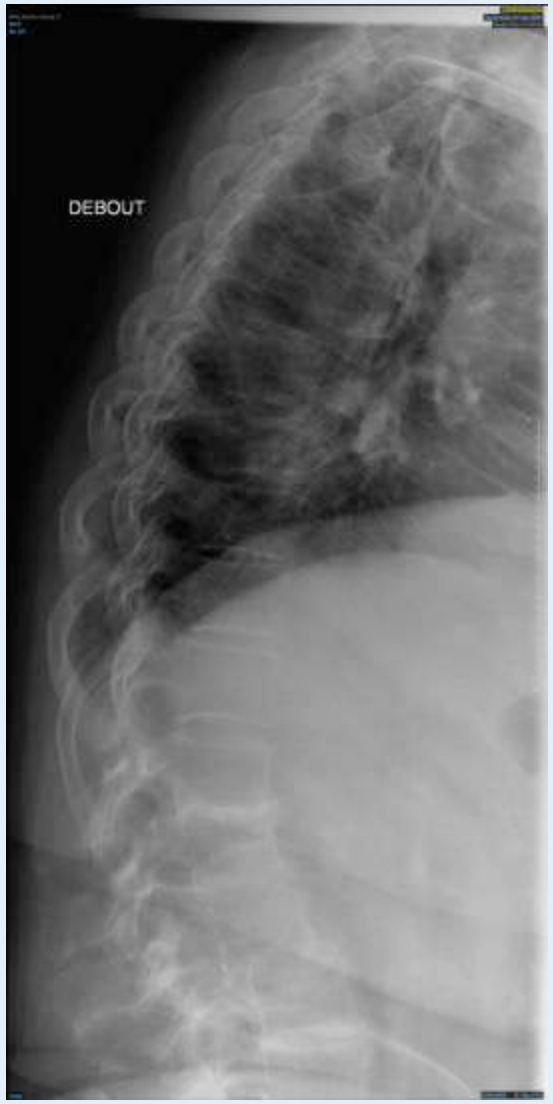
DT2

Réponse insuffisante à Metformine

Sous inhibiteurs SGLT2

Chute avec dorsolombalgie intense

Cas clinique 2



Cas clinique 2

Lesquels des traitements suivants peuvent favoriser la perte de masse osseuse ?

1. **Insuline**
2. **Metformine**
3. **Analogues GLP-1**
4. **Inhibiteurs SGLT-2**
5. **Corticoïdes**

Cas clinique 2

Lesquels des traitements suivants peuvent favoriser la perte de masse osseuse ?

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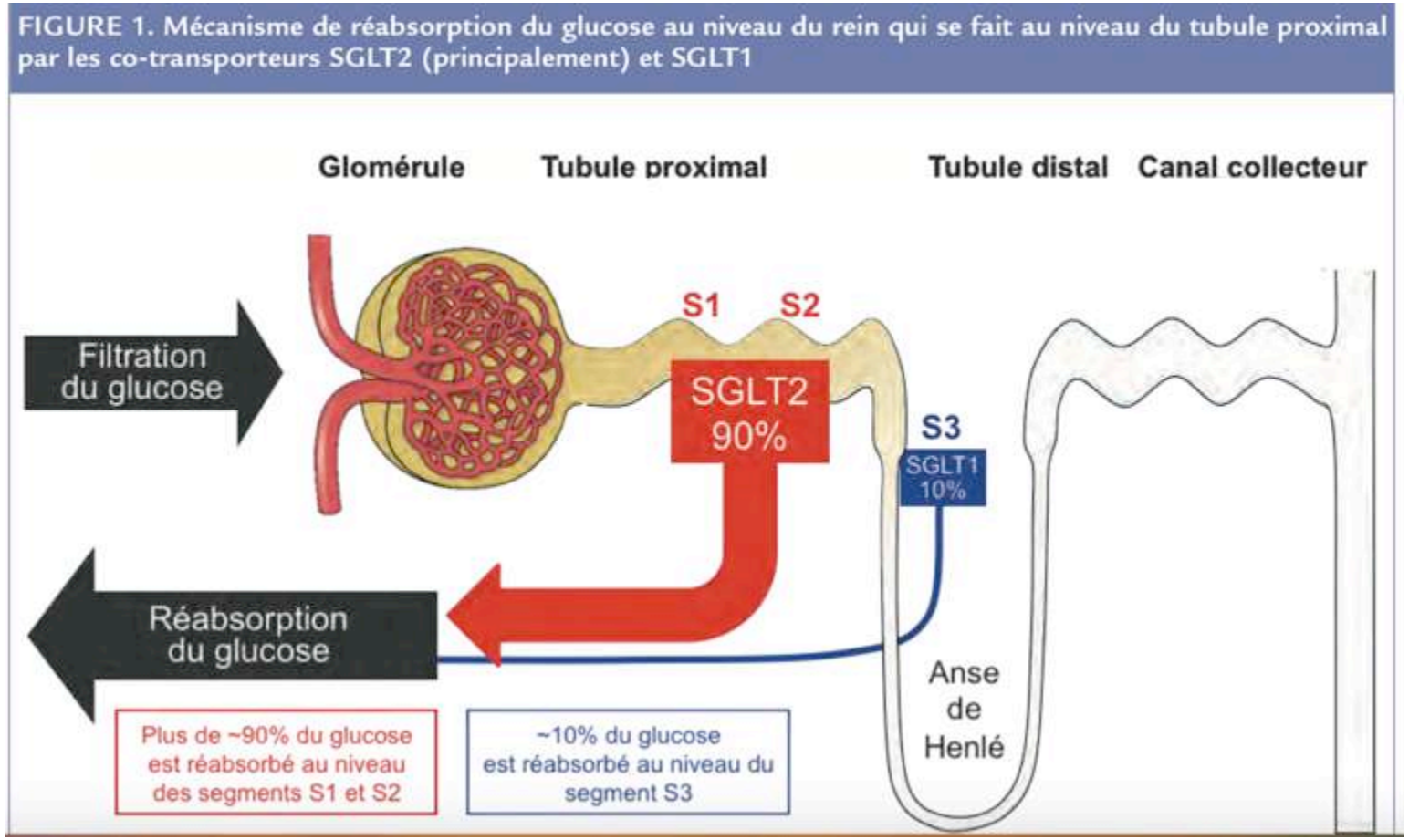
Inhibiteurs du SGLT-2

- **Co-transporteur sodium/glucose type 2**
- **Tubules rénaux proximaux = réabsorption 90% glucose filtré**
- **Inhibiteurs induisent glycosurie +++**

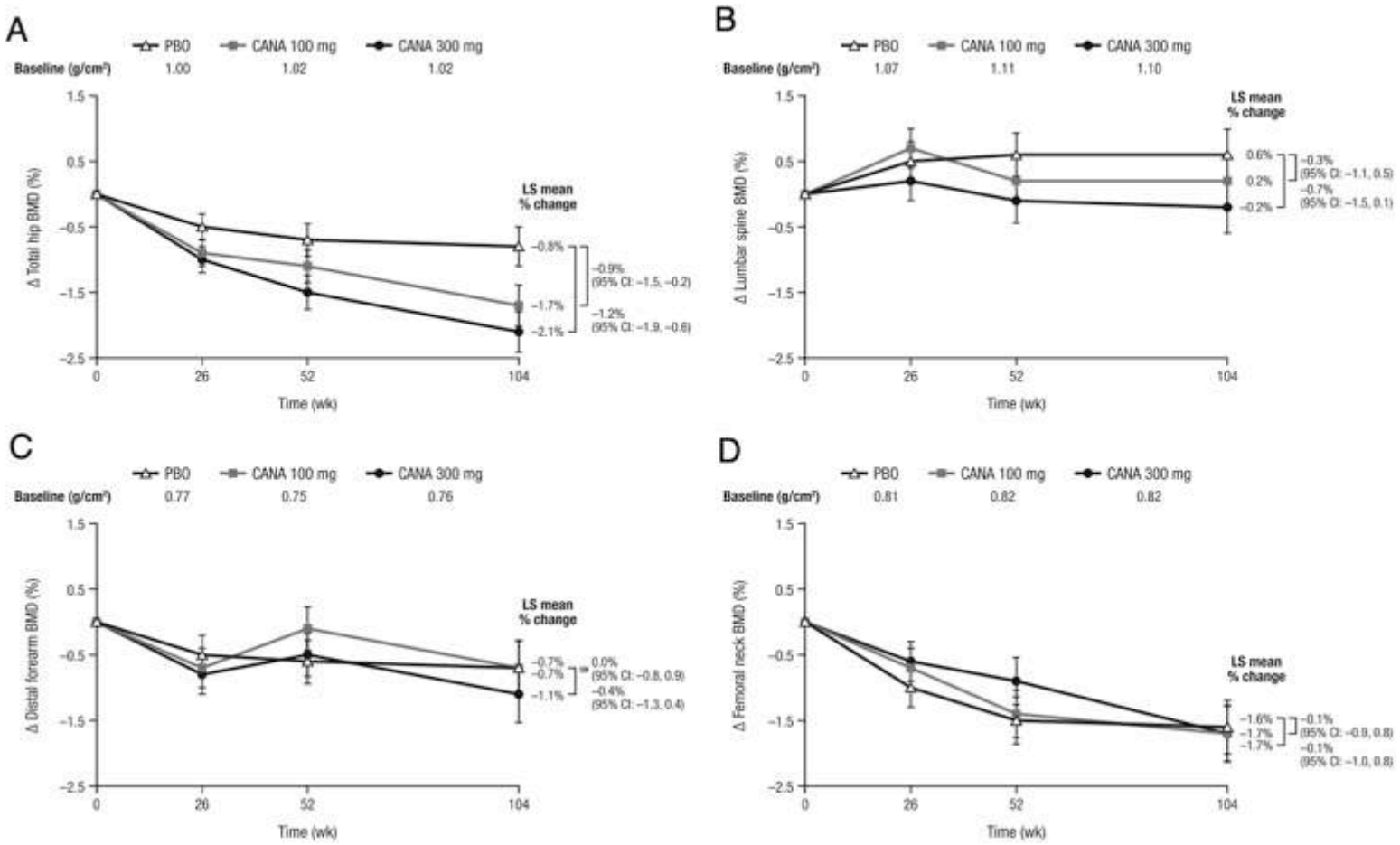


Penfornis et al. Cordiam 2016

Inhibiteurs du SGLT-2

Effets osseux

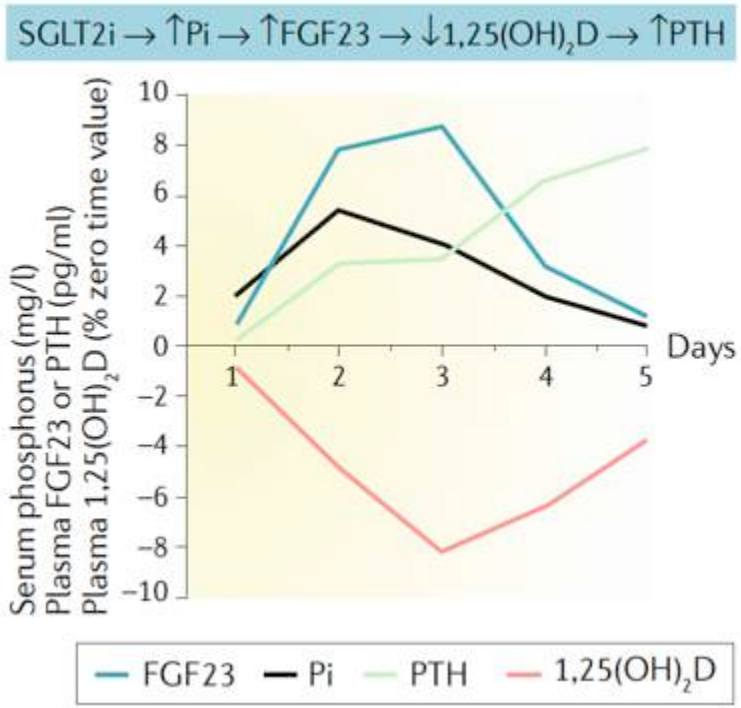
- 9.4% fractures sous dapaglifozin
- Baisse DMO sous canaglifozin

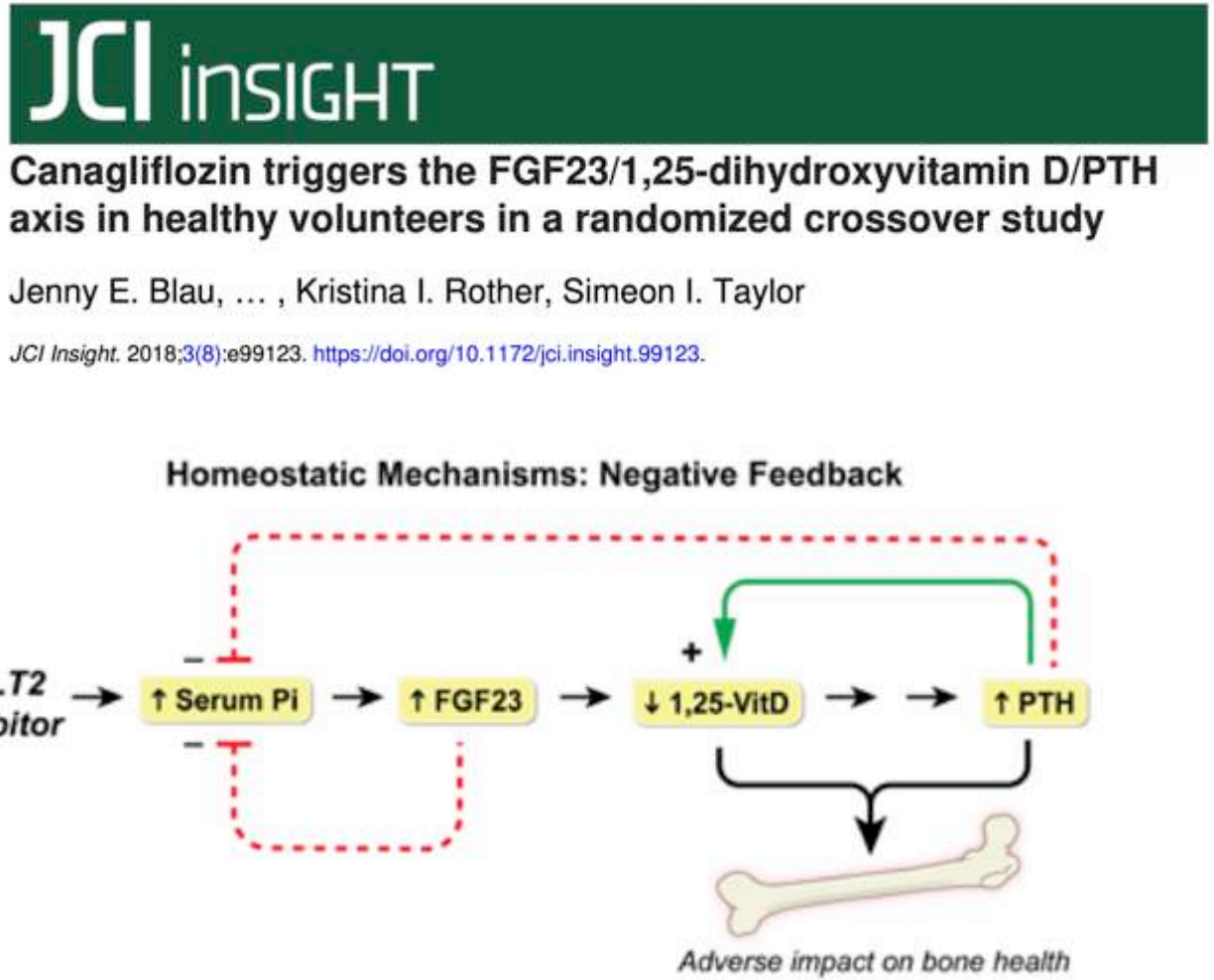


Kohan D et al. Kidney Int 2014 / Bilezikian JP et al. JCEM 2016

Inhibiteurs du SGLT-2

Effets osseux





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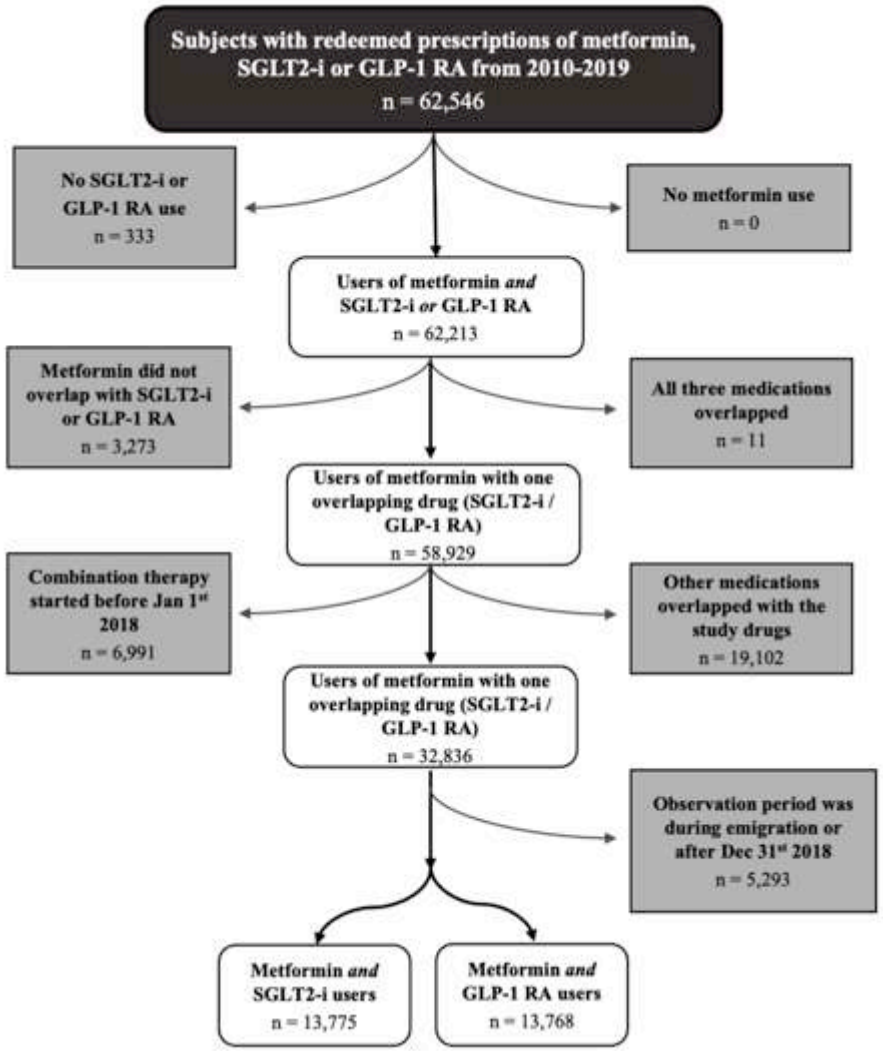
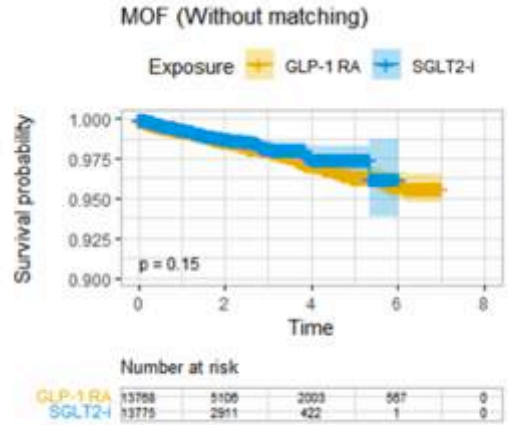
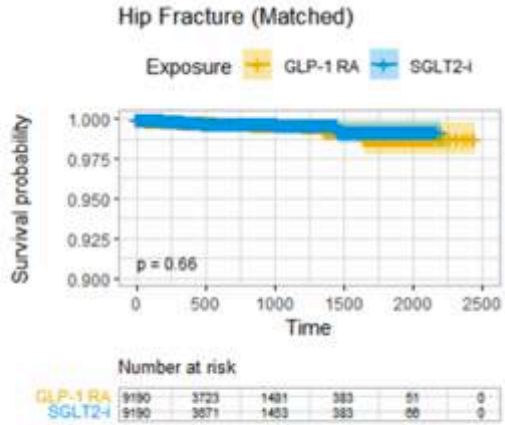
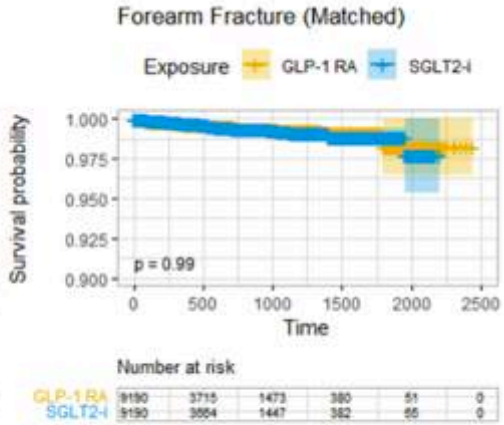
SGLT2 inhibitor treatment is not associated with an increased risk of osteoporotic fractures when compared to GLP-1 receptor agonists: A nationwide cohort study

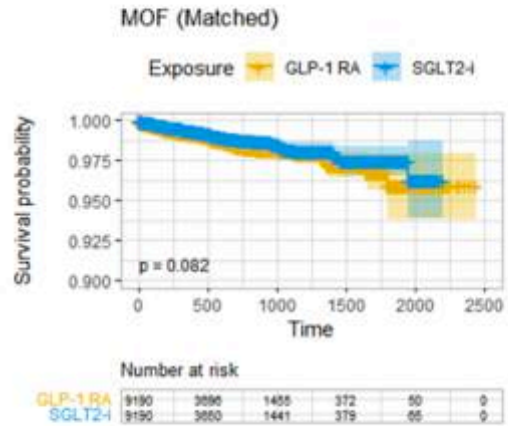
Zheer Kejlberg Al-Mashhadi[1,2*†], Rikke Viggers[3,4†], Jakob Starup-Linde[1,2,5], Peter Vestergaard[3,4] and Søren Gregersen[1,2]

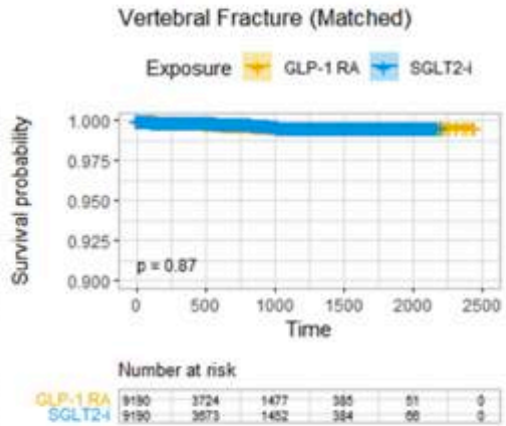

Subjects with redeemed prescriptions of metformin, SGLT2-i or GLP-1 RA from 2010-2019
n = 62,546
No SGLT2-i or GLP-1 RA use
n = 333
No metformin use
n = 0
Users of metformin and SGLT2-i or GLP-1 RA
n = 62,213
Metformin did not overlap with SGLT2-i or GLP-1 RA
n = 3,273
All three medications overlapped
n = 11
Users of metformin with one overlapping drug (SGLT2-i / GLP-1 RA)
n = 58,929
Combination therapy started before Jan 1st 2018
n = 6,991
Other medications overlapped with the study drugs
n = 19,102
Users of metformin with one overlapping drug (SGLT2-i / GLP-1 RA)
n = 32,836
Observation period was during emigration or after Dec 31st 2018
n = 5,293
Metformin and SGLT2-i users
n = 13,775
Metformin and GLP-1 RA users
n = 13,768

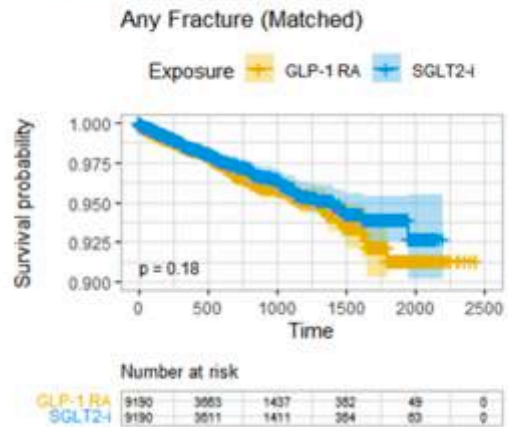

MOF (Without matching)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.15
Time
Number at risk
GLP-1 RA 13768 5106 2003 567 0
SGLT2-i 13775 2911 422 1 0

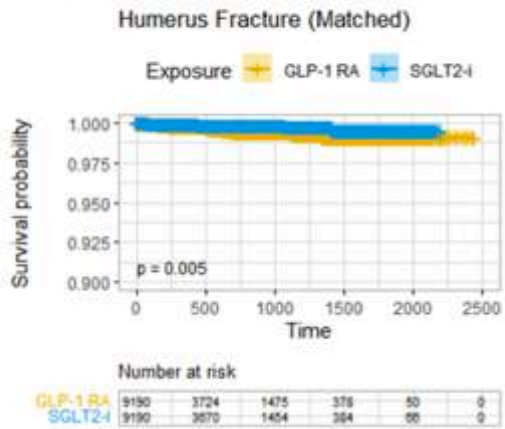

Hip Fracture (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.66
Time
Number at risk
GLP-1 RA 9190 3723 1481 383 51 0
SGLT2-i 9190 3671 1463 383 66 0


Forearm Fracture (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.99
Time
Number at risk
GLP-1 RA 9190 3715 1473 380 51 0
SGLT2-i 9190 3664 1447 382 66 0


MOF (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.082
Time
Number at risk
GLP-1 RA 9190 3696 1455 372 50 0
SGLT2-i 9190 3660 1441 379 66 0


Vertebral Fracture (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.87
Time
Number at risk
GLP-1 RA 9190 3724 1477 385 51 0
SGLT2-i 9190 3673 1452 384 66 0


Any Fracture (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.18
Time
Number at risk
GLP-1 RA 9190 3663 1437 362 49 0
SGLT2-i 9190 3611 1411 364 63 0


Humerus Fracture (Matched)
Exposure GLP-1 RA SGLT2-i
Survival probability
p = 0.005
Time
Number at risk
GLP-1 RA 9190 3724 1475 378 50 0
SGLT2-i 9190 3670 1454 384 66 0

Lupus et sGLT2

- **Atteinte rénale sévère**
- **Risque d'ins rénale malgré CTC/IS**
- **Protecteur IEC**

- **sGLT2 : protecteur CV et rénale chez le diabétique**
- **Réduction pression intra glomérulaire ?**

Lupus et sGLT2

Données préliminaires sur 5 patients SLE : réduction 50% protU

Table 1 Main effects of sodium–glucose cotransporter-2 inhibitors (empaglifozin 10 mg) lupus nephritis

N	Age/sex	Classification LN (ISN/RPS 2003)	IMS (doses mg/day)	RAASi (doses mg/day)	GFR baseline (mL/min/1.73 m^2)	GFR 8 weeks (ml/min/1.73 m^2)	Proteinuria baseline (g/day)	Proteinuria 8 weeks (g/day)	Serum albumin baseline (g/dL)	Serum albumin 8 weeks (g/dL)
1	63/F	V	S 2.5+MPA 980	Enalapril 20+SPR 25	53	44	1.8	0.9	4.2	4.1
2	59/F	IIIA	MPA 1600	Telmisartan 80+SPR 25	65	60	1.9	0.8	4.2	4.5
3	46/F	V	S 2.5+MMF 1250	Irbesartan 150+SPR 25	89	74	0.62	0.27	3.9	4.3
4	32/F	1-IVAG+V 2-IVAG	S 5+MPA 720	Telmisartan 80	34	30	5.96	3.7	2.7	3.5
5	46/F	1-V 2-IVS (A,C)+V	S 5+MPA 1080	Enalapril 10+SPR 25	94	90	0.76	0.39	3.8	4.2

F, female; GFR, glomerular filtration rate; IMS, immunossupression; LN, lupus nephritis; MMF, mycofenolate mofetil; MPA, mycophenolic acid; RAASi, renin-angiotensin-aldosterone inhibitors; S, steroids; SPR, spironolactone.

Lupus et sGLT2

Systemic lupus erythematosus

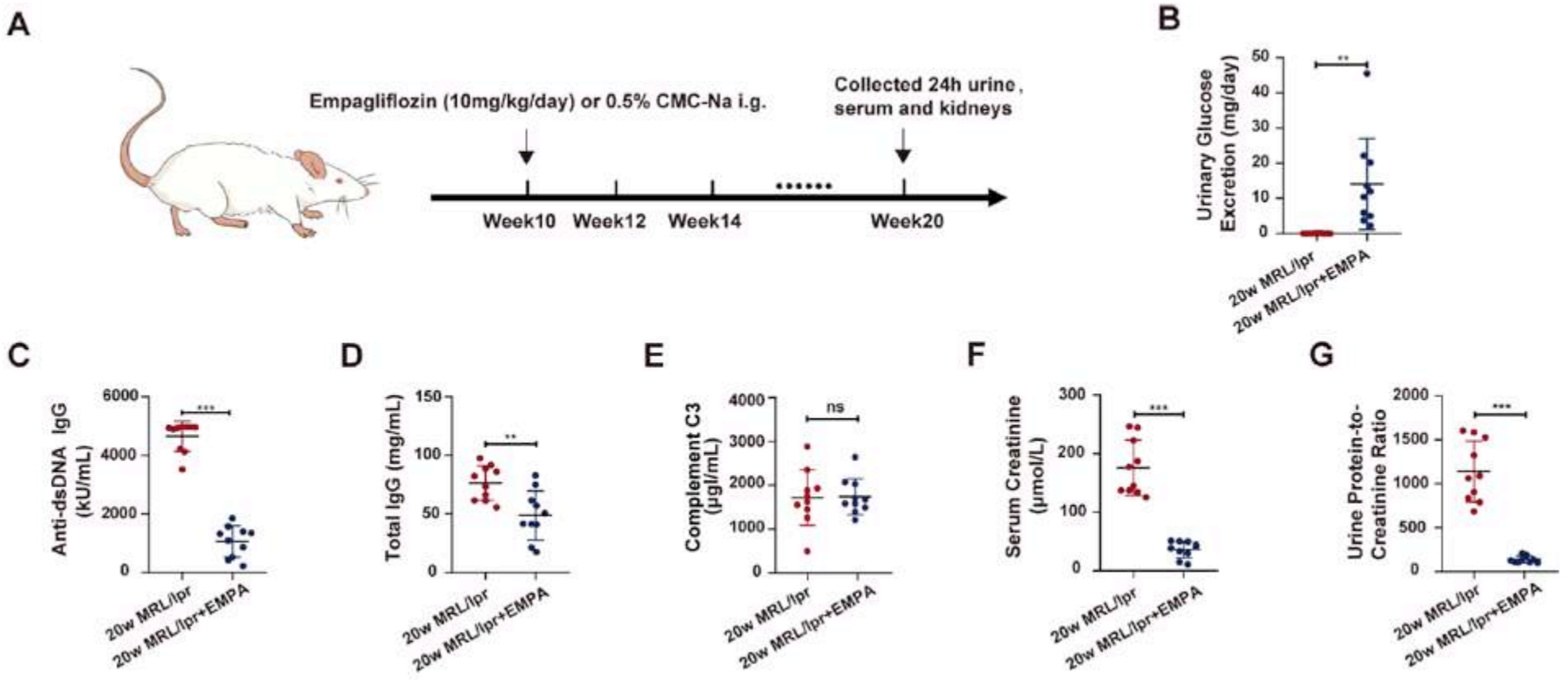
TRANSLATIONAL SCIENCE

SGLT2 inhibitors alleviated podocyte damage in lupus nephritis by decreasing inflammation and enhancing autophagy

Xin-yu Zhao,[1,2] Shuang-shuang Li,[1,2,3,4] Ying-xin He,[1,2,3,4] Li-jie Yan,[1,2,3,4] Fu Lv,[1,2] Qi-meng Liang,[1,2] Yu-hui Gan,[1,2,3,4] Li-pei Han ,[1,2] Hong-de Xu,[2,4] Yong-chun Li,[2,4] Yuan-yuan Qi [1,2,5]

Lupus et sGLT2

- **Effet spectaculaire chez la souris « lupus-like »**



Lupus et sGLT2

- **Confirmation effet positif chez des patients en rétrospectif**

Table 1 Clinical features, treatments strategies and effects for patients with LN treated with SGLT2 inhibitors

				Baseline							Follow-up				
N	Age (years)*	Gender	Classification of LN	IMS (doses/day)	RAASi (doses/day)	eGFR(mL/min/1.73 m^2)	Proteinuria (g/day)	Serum albumin (g/dL)	SGLT2 (doses/day)	Duration of follow-up (week)	IMS (doses/day)	RAASi (doses/day)	eGFR(mL/min/1.73 m^2)	Proteinuria (g/day)	Serum albumin (g/dL)
1	33	F	V	Methylprednisolone 24mg+cumulative CYC 0.7g		98.4	1.35	32.8	Dapagliflozin 10mg	11	Methylprednisolone 12mg+cumulative CYC 1.1g		121.0	0.95	39.7
2	25	M	IV	Prednisone 30 mg	Allisartan isoproxil 240mg	64.1	3.08	36.0	Dapagliflozin 10mg	12	Prednisone 30 mg	Allisartan isoproxil 240 mg	99.2	0.60	42.3
3	30	M	IV	Prednisone 37.5 mg+MMF1000 mg	Valsartan 80mg	92.2	0.78	33.9	Dapagliflozin 10 mg	15	Prednisone 22.5 mg+MMF1000 mg	Valsartan 80 mg	92.7	0.40	43.4
4	45	F	V	Methylprednisolone 14mg+TAC 3 mg	Allisartan isoproxil 240 mg	87.4	0.58	33.9	Canagliflozin 100 mg	17	Methylprednisolone 8mg+TAC 3 mg	Allisartan isoproxil 240mg	105.5	0.32	37.6
5	31	F	V	Prednisone 45mg+TAC 2 mg		126.8	1.83	37.9	Dapagliflozin 10mg	12	Prednisone 22.5 mg+TAC 2 mg		131.6	0.73	35.4
6	25	M	IV	Prednisone 22.5 mg+MMF 1000mg+TAC 2 mg	Valsartan 80mg	124.7	8.19	37.4	Dapagliflozin 10mg	16	Prednisone 15mg+MMF 1000mg	Valsartan 80 mg	121.2	4.50	41.8
7	32	F	IV	Prednisone 60mg		63.6	4.30	16.5	Canagliflozin 100 mg	21	Prednisone 50mg		120.3	1.47	26.8
8	55	F	IV	Methylprednisolone 20mg+cumulative CYC 0.6g	Allisartan isoproxil 240mg	59.9	6.72	28.2	Canagliflozin 100 mg	11	Methylprednisolone 12mg+cumulative CYC 2.2g	Allisartan isoproxil 240 mg	74.6	0.25	42.9
9	57	F	V	Prednisone 30mg+cumulative CYC 1.0g	Sacubitril/valsartan 100mg	104.2	1.58	39.5	Ertugliflozin 5 mg	18	Prednisone 15mg+cumulative CYC 5.8g	Sacubitril/valsartan 100mg	110.0	0.66	41.4

*Age with the first dose of SGLT2 inhibitors.
CYC, cyclophosphamide; F, female; IMS, immunosuppression; LN, lupus nephritis; M, male; MMF, mycophenolate mofetil; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2, sodium glucose cotransporter 2; TAC, tacrolimus.

Lupus et sGLT2

- **Démonstration des mécanismes**
  - Expression tubules et glomérules
  - Activation autophagie (↘ mTORC)
  - Réduction de l'inflammasome NLRP3 (sur podocytes)
- **sGLT2 inh : futur TT ?**

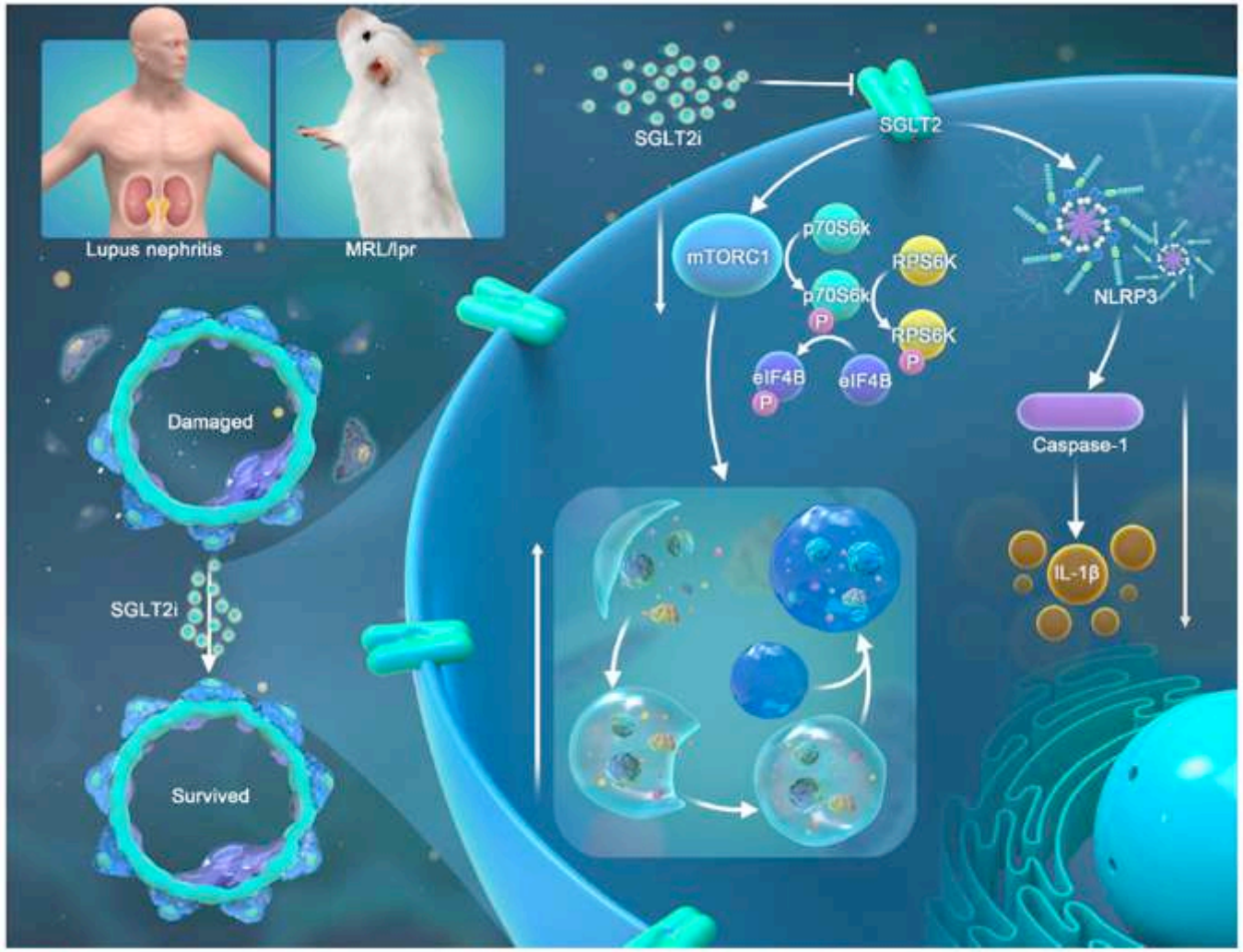


Figure 6 SGLT2 inhibitors alleviated podocyte damage in lupus nephritis by decreasing inflammation and enhancing autophagy.

Conclusions

- Nouveaux antidiabétiques / Obésité
  - Regardez les ordonnances de vos patients !
  - Analogues GLP-1
  - Inhibiteurs SGLT-2
  - Élargissement des indications aux comorbidités ?
  - Quid des effets sur micro-inflammation RIC ?
  - Potentiel dans le lupus ?