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► To cite this version:

Chaohua Deng, Arnaud Bianchi, Nathalie Presle, David Moulin, Meriem Koufany, et al.. Eplerenone treatment alleviates the development of joint lesions in a new rat model of spontaneous metabolic-associated osteoarthritis. *Annals of the Rheumatic Diseases*, 2018, 77 (2), pp.315 - 316. 10.1136/annrheumdis-2016-210700 . hal-01702028

HAL Id: hal-01702028

<https://hal.univ-lorraine.fr/hal-01702028v1>

Submitted on 18 Feb 2022

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**EPLERENONE TREATMENT ALLEVIATES THE DEVELOPMENT OF JOINT
LESIONS IN A NEW RAT MODEL OF SPONTANEOUS
METABOLIC-ASSOCIATED OSTEOARTHRITIS**

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Increasing epidemiological and clinical studies suggest that metabolic syndrome (MetS) plays a role in the incidence and progression of osteoarthritis (OA).[1,2] However, in absence of appropriate MetS-associated OA experimental model,[3] the MetS contribution to the joint phenotype in OA remains difficult to investigate and the evaluation of potential disease-modifying OA drugs (DMOADs) is complicated. Noteworthy, in contrast to their lean SHHF^{+/+} (spontaneously hypertensive heart failure) controls, obese SHHF^{cp/cp} rats, a well-characterized model of MetS,[4] develop drastic metabolic, cardiovascular and renal alterations that are substantially improved through an early chronic mineralocorticoid receptor antagonism (MRA) treatment.[5] Thus, by comparing young (1.5 months) and aged (12.5 months) lean SHHF^{+/+} and obese SHHF^{cp/cp} rats, we sought to evaluate for the first time the potential i) contribution of MetS to joint alterations and ii) therapeutic benefits derived from chronic MRA treatment by eplerenone (Fig1A).

Rats with no MetS (^{1.5}SHHF^{+/+} and ^{12.5}SHHF^{+/+}) or with barely developed MetS (^{1.5}SHHF^{cp/cp})[4] displayed normal knee articular phenotype (Fig1Ba,e,i,m and data not shown for young rats). In striking contrast, ^{12.5}SHHF^{cp/cp} rats, affected by culminating MetS conditions,[4] exhibited knee joints with marked fibrillations from the surface to the middle layer of the cartilage (Fig1Bc,g,k) and moderate to severe loss of proteoglycans (Fig1Bg) and collagen II (Fig1Bk) through the entire thickness of the cartilage. These alterations of the ^{12.5}SHHF^{cp/cp} knees were associated with pronounced osteophyte formation (Fig1Bc,k) and with fibrosis, inflammation and cellular infiltration of the synovial tissue (Fig1Bc,o). Very interestingly, we could demonstrate that a preventive 11-month eplerenone treatment did not alter the normal knee phenotype of ^{12.5}SHHF^{+/+} rats (Fig1Bb,f,j,n) but substantially reduced the cartilage damages, osteophyte formation and synovial inflammation observed in placebo ^{12.5}SHHF^{cp/cp} rats (compare Fig1Bd,h,l,p with Fig1Bc,g,k,o respectively). Those striking findings were further substantiated by cartilage degeneration, osteophyte formation and synovial membrane inflammation scores, measured according to the last OARSI recommendations for histological assessments in rats[6] (Fig1C). Altogether, this establishes that metabolic disorders in obese SHHF^{cp/cp} rats induce changes in the knee joint that are significantly prevented upon chronic treatment with MRA eplerenone.

Stratifying OA of various etiologies to attain precision medicine[7] is yet of limited interest as no efficient and specific DMOAD is available for clinical use.[3,7] In this regard, the present pilot study sustains the proof-of-concept that preventive and chronic MRA treatment with the well-known safety profile drug eplerenone may constitute a promising therapeutic strategy effective for MetS patients at increased risk of developing knee OA, especially those with abdominal obesity we very recently reported to be better responder to eplerenone.[8] Interestingly, through the known beneficial impact of eplerenone on cardiac[5] and renal (unpublished data) conditions, plus the hereby supported positive effect on the development of MetS-associated cartilage and synovial lesions, MRA could ease mobility of this subfamily of OA patients. If validated in clinic, such improvement of their life quality might further participate to the decrease of cardiovascular risks in MetS patients by maintaining physical activity.

In conclusion, we uncovered the SHHF^{cp/cp} strain as a unique spontaneous MetS-associated OA model in rat. Although the bone phenotype remains to be characterized, our work highlights the SHHF model as a novel and attractive instrumental tool to evaluate new preventive and curative therapeutics. Actually, using this model, we evidenced that preventive chronic MRA could positively impede the development of OA-like lesions in the articular and synovial tissues of individuals with MetS. Current and future investigations *in vitro*, in SHHF model and in patients cohorts will help decipher which and how systemic and/or local modulations of MR-downstream pathways[9] are involved in this uncovered beneficial effect of eplerenone in MetS-induced OA lesions.

Acknowledgments

This work was supported by Inserm and Région Lorraine.

The sponsors had no role in any experimental part of the study or the writing of the manuscript.

Contributions

HK and AP conceived the study; CD, AB, NP, DM, MK, CG and AP performed the experiments; CD, AB, NP, DM, MK, HK and AP interpreted the data; CD, HK and AP wrote the manuscript.

Competing interests

None

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