International Journal of Peptide Research and Therapeutics (2022) 28: 140
https://doi.org/10.1007/s10989-022-10448-4

Urotensin-II Prevents Cartilage Degeneration in a Monosodium Iodoacetate-Induced Rat Model of Osteoarthritis

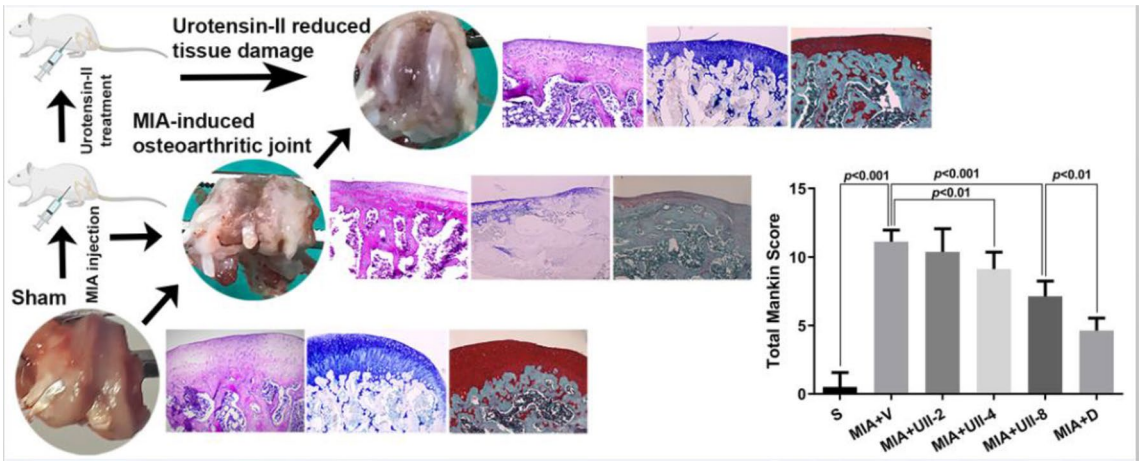
Menderes Yusuf Terzi[1,2] · Hamza Malik Okuyan[3] · İhsan Karaboğa[4] · Cemil Emre Gökdemir[5] · Duygu Tap[2] · Aydıner Kalacı[5]

Accepted: 23 July 2022 / Published online: 9 August 2022

Abstract

Osteoarthritis (OA) is a common degenerative articular disorder caused by traumatic or spontaneous factors such as genetics, obesity, and advanced age. Comprehending the pathogenic mechanism of OA ensures the development of novel disease-modifying therapeutics rather than conventional palliative drugs with undesired side effects. Urotensin-II (UII) is a multi-functional short cyclic peptide implicated in several disorders. We aimed to analyze the effects of intraarticular UII treatment in a monosodium iodoacetate (MIA)-induced OA rat model. We divided animals into six groups to test three different concentrations of UII with histopathological and immunohistochemical analyses of bone morphogenetic protein-2 (BMP-2), nuclear factor kappa B subunit 1 (NF-κB), and intrinsic UII expression. We analyzed serum levels of cartilage related and inflammatory markers post-OA. We observed a noticeable amelioration of the MIA-induced knee damage in UII-treated animals after gross morphology examination. Mankin scoring after histopathological stainings revealed a partial prevention of articular tissue damage in UII-treated animals. We found a significant reduction in BMP-2 and NF-κB while an increase in intrinsic UII expressions upon exogenous UII injection after immunohistochemical analyses. The Mankin scores were significantly correlated with BMP-2, NF-κB, and intrinsic UII levels. There was no significant alteration in serum markers after UII treatment. We are the first group showing the protective effect of UII on the destructed knee joints of osteoarthritic rats by downregulating the BMP-2 and NF-κB and upregulating intrinsic UII expressions. To uncover the mechanistic role of UII during OA, further experiments are warranted.

Graphical Abstract



Keywords Osteoarthritis · Urotensin-II · Cartilage destruction · Monosodium iodoacetate · BMP-2 · NF-κB

Extended author information available on the last page of the article

Abbreviations

OA	Osteoarthritis
UII	Urotensin-II
BMP-2	Bone morphogenetic protein 2
NF-κB	Nuclear factor kappa B subunit 1
COMP	Cartilage oligomeric matrix protein
IL-6	Interleukin-6
IL-1β	Interleukin-1β
ELISA	Enzyme-linked immunosorbent assay

Introduction

Osteoarthritis (OA) is a prevalent arthritic disorder affecting more than 300 million people worldwide annually (Disease et al. 2018). The incidence of aging-related disorders including OA is projected to rise in parallel with prolonged life expectancy owing to the improvements in the healthcare system (Lunenfeld and Stratton 2013). The main pathological features of OA are cartilage destruction, synovial inflammation, fibrillation, ulceration, and degradation of the articular matrix, and destruction of the joint upper layer, which results in osteophyte formation, the thickness of subchondral bone, and the resultant pain (Felson 2006; Mobasheri and Batt 2016). Although several risk factors including genetics, aging, obesity, and trauma have been known to contribute to the onset of OA, its molecular pathogenesis has not been fully understood yet (Geyer and Schonfeld 2018).

OA animal models are common tools to study the pathophysiology of the disease that is a surrogate of human OA. Monosodium iodoacetate (MIA) functions as glyceraldehyde-3-phosphate dehydrogenase inhibitor that hinders glycolysis and causes cell death in chondrocytes (Kuyinu et al. 2016). MIA-induced OA model belongs to the chemically induced OA and is commonly preferred by researchers over other models (spontaneous or traumatic) due to its reproducibility (Teeple et al. 2013).

Today, the therapeutic options for the treatment of OA are aiming at either relieving the pain with drugs as a palliative option or lasting operational joint replacement due to the lack of non-invasive options for permanent rehabilitation (Cao et al. 2020). Therefore, understanding the molecular pathogenesis underlying OA and discovering the disease-modifying therapies are essential to improve the quality of life of the patients with OA and to reduce the socioeconomic costs of OA (Kim et al. 2018).

Urotensin-II (UII) is an 11–17 amino acid-long peptide with a functional cyclic part that is conserved among various species (Sun and Liu 2019). UII plays a vital role in the vascular system by functioning as a strong vasoconstrictor or vasodilator, which is abundantly expressed in the cardiovascular system, kidneys, and central nervous system amongst other tissues and organs (Ross et al. 2010). UII is involved in not only vaso-modulatory activities but also several physiological and pathological conditions (Sun and Liu 2019). UII and its G protein-coupled receptor-14 (UTR) have been implicated in the pathways pertaining to the inflammatory responses of atherosclerosis and colonic inflammation through bone morphogenetic protein-2 (BMP-2) and nuclear factor kappa B subunit 1 (NF-κB) pathways (McDonald et al. 2007; Yang et al. 2016). Besides, the increased levels of UII in synovial fluids (SF) of OA patients were also reported in a previous clinical study (Gogebakan et al. 2014). Previous studies investigating the action mechanisms of UII highlight the diagnostic and therapeutic importance of this molecule in pathophysiological conditions (Ross et al. 2010; Pereira-Castro et al. 2019). Of which, some studies claim that UII contribute and/or exacerbate fibrosis via mostly recruiting or corroborating the inflammatory pathways in different disease models affecting lung, liver, and heart (Zhang et al. 2007; Kemp et al. 2009; Onat et al. 2012). On the contrary, some other studies report that UII exhibits protective effects mainly by attenuating apoptosis in kidney, heart, and endothelial cells (Chen et al. 2012, 2014; Hsu et al. 2013). However, the underlying action mechanism of this multifunctional vasoactive peptide is still obscure during OA pathogenesis. In this present study, we aimed to investigate the potential therapeutic effects of exogenous UII administration articularly in MIA-induced OA rat model. For this objective, we conducted analyses to check histopathological and immunohistochemical alterations in the central molecules pertaining to inflammation and chondrocyte and bone metabolisms pathways i.e., BMP-2 and NF-κB (Goldring and Marcu 2009) as well as the vasomodulatory peptide UII. We also performed ELISA assays to detect serum levels of prominent inflammatory cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β) and a prominent bone/cartilage pathophysiology biomarker; cartilage oligomeric matrix protein (COMP) after intra-articular UII treatment.

Methodology

Experimental Animals

All experimental procedures in the present work were abided by the "Animal Care and Use Committee Guidelines" of Hatay Mustafa Kemal University as an act of animal protection utilized for scientific aims. Before the experiments, institutional ethical approval was acquired from the "Animal Ethics Committee of Hatay Mustafa Kemal University" (2020/4–18). We conducted all experiments with a total of 40 male Wistar albino rats weighing 350–400 g and aging 4 months, which were allowed to reach food and water ad-libitum. The animals were kept in solid-bottom cages under 23 ± 2 °C, 60–80% humidity and 12-h light/dark cycle

conditions with regularly refreshed ventilation. Prior to the start of the experiments, all animals were kept in their cages for about one week for environmental adaptation.

OA Model Induction via MIA Injection and Treatment Regimes

We divided 40 rats into 5 individual cages comprising eight animals per group. In order to model OA in animals, at day 0 (zero), a single dose of 0.1 mg/µl (25 µl) MIA (M, Sigma–Aldrich, USA) was administered into the infrapatellar ligament of the right knee with a 26.5-G needle (Guzman et al. 2003) under isoflurane-mediated (Hana Pharm, Korea) anesthesia via inhalation (Bove et al. 2003). Fifteen days after the initial MIA injection (or saline as a vehicle) when the fibrosis starts to progress in the knee joint (Guzman et al. 2003), the animals were treated with UII (U7257, Sigma Aldrich, MO, USA) or saline via intra-articular injection at every 3 days for a total of seven injections (Kim et al. 2016) or with 2 mg/kg diclofenac (D, positive control) subcutaneously on daily basis for 21 days. The animal groups were designated as follow (Fig. 1): Group-1 (S): Sham; a single injection of 25 µl saline solution intra-articularly into the right knee and 7 intra-articular injections of 25 µl saline; Group-2 (MIA + V): MIA + Vehicle; a single dose of intra-articular MIA injection and 7 intra-articular injections of 25 µl saline; Group-3 (MIA + UII-2), Group-4 (MIA + UII-4), and Group-5 (MIA + UII-8): A single dose of MIA via intra-articular injections and 7 injections of 2, 4, and 8 µg UII in 25 µl saline solution respectively (Wu et al. 2010; Okuyan et al. 2021); Group-6 (MIA + D): MIA + diclofenac; a single dose of MIA via intra-articular injection and daily diclofenac treatment for 21 days.

All animals were sacrificed at day 37 via deep anesthesia for further histopathological, immunohistochemical, and ELISA analyses. For the latter, the sera were collected from the whole bloods of the rats via cardiac puncture by spinning down at 2000 × g for 10 min at 4 °C.

Histopathological Analysis

After the morphological examination, knee samples were put into 10% formalin solution for fixation about 3 days and incubated in 10% EDTA (Sigma Aldrich) for 4 weeks at room temperature for decalcification (Lu et al. 2018). Then, the samples were run through within ascending ethanol series and in absolute xylene for dehydration and finally were embedded in paraffin wax. For histopathological and immunohistochemical analyses, 5-µm-thick paraffin sections were sliced with a rotary microtome (CUT-5062, Slee MeDal, Mainz, Germany). Then, the tissue sections were stained with hematoxylin and eosin (H&E) for general cellular structure, safranin O and fast green FCF for collagen and proteoglycan amount, and toluidine blue for glycosaminoglycan amount (Dumond et al. 2004; Lu et al. 2018). Finally, the stained tissue sections were photographed with a light microscope (Olympus CX41, Tokyo, Japan) for further analyses using an image analysis software (Kameram Gen III, Argenit, Istanbul, Turkey). In safranin O & fast green FCF stained slides, medial tibial plateaus were examined for the cartilage degeneration and evaluated using the Mankin scoring system (Mankin 1971) with a scale ranging between 0 and 14 points (0 = No cartilage degeneration, 14 = Severe cartilage degeneration) by two experts blinded to groups (Table 1).

Immunohistochemical Examination

For NF-κB, BMP-2, and UII immunohistochemical examinations, tissue sections were deparaffinized in xylene, passed through descending ethanol series for rehydration, and rinsed with phosphate-buffered saline (PBS). Then, the sections were washed in 3% hydrogen peroxide solution to block endogenous hydrogen peroxidase activity causing non-specific background staining. Thereafter, the sections were boiled in citrate buffer solution for antigen retrieval. Next, after the slides were washed in PBS and incubated with blocking serum at room temperature for 1 h, they were

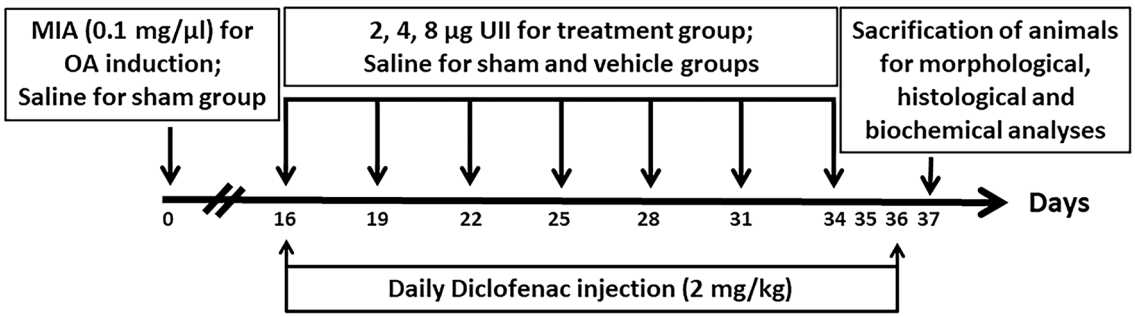


Fig. 1 Design of the experimental procedure. *MIA* Monosodium iodoacetate, *OA* Osteoarthritis, *UII* Urotensin-II

Table 1 Mankin score grading system for osteoarthritic articular cartilage (Mankin 1971)

Category	Subcategory	Score
Structure	Normal	0
	Surface irregularities	1
	Pannus and surface irregularities	2
	Clefts to transitional zone	3
	Clefts to radial zone	4
	Clefts to calcified zone	5
	Complete disorganisation	6
Cells	Normal	0
	Diffuse hypercellularity	1
	Cloning	2
	Hypocellularity	3
Safranin O staining	Normal	0
	Slight reduction	1
	Moderate reduction	2
	Severe reduction	3
	No dye noted	4
Tidemark integrity	Intact	0
	Crossed by blood vessels	1
Total		0–14

further incubated with anti-BMP-2 (YID0638, YL Biont, Shanghai, China), anti-NF-κB (NB100-56,055, Novus Biologicals, Littleton, CO, USA), and anti-UII (Biorbyt Ltd, Cambridge, UK) primer antibodies (Nf-κβ and BMP-2; 1:100, UII; 1:20 dilutions) in a humidified chamber for 60 min at 37 °C. Following incubation, biotinylated secondary antibody and streptavidin peroxidase (Ultra Vision Detection System-HRP kit, Thermo Scientific/Lab Vision, Fremont, CA, USA) were applied to the slides respectively for 20 min at room temperature. Slides were washed in PBS and treated with 3-amino-9-ethylcarbazole (AEC, Thermo Scientific/Lab Vision) as chromogenic substrate. Contrast staining was performed with Mayer's hematoxylin. The UII, NF-κB and BMP-2 stainings were evaluated with an image analysis software (Kameram Gen III, Argenit, Istanbul, Turkey). The staining intensities of UII, NF-κB and BMP-2 were quantitatively assessed by integrated optical density measurement method (Okuyan et al. 2020).

Measurement of Serum Protein Levels via ELISA

Serum levels of COMP, IL-6, and IL-1β were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits following manufacturers' protocols. The intra-assay and inter-assay coefficients of variations for COMP (Elabscience), IL-6 (Invitrogen), and IL-1β (Invitrogen) were 8% and 5%, 10% and 12%, and 10% and 10% respectively. The sera samples with hemolysis were excluded from the analyses.

Statistical Analysis

We utilized Shapiro–Wilk test to check whether our data were normally distributed. The significant differences among the groups were tested with parametric one-way ANOVA or non-parametric Kruskal–Wallis H tests. Individual groups were compared via two-way comparison by using non-parametric Mann–Whitney U test or parametric Holm-Sidak's multiple comparison tests. The correlation analyses were conducted with Spearman's correlation test since normal distribution was not met. We utilized SPSS package software (version 22.0) for all statistical analyses and Graphpad (version 8.0.2) for setting plots. The data were expressed as mean ± standard deviation or mean ± standard error of the mean. We accepted p values less than 0.05 as statistically significant.

Results

Macroscopic Observations

The gross morphologic analyses of the articular surfaces of rats' knee joints were depicted in Fig. 2. MIA administration clearly destructed the cartilage and subchondral bone in MIA + V group compared to the intact and healthy tibial plateau and the femoral condyle in the sham group. UII-treated osteoarthritic rats (MIA + UII-2,-4, and -8) prevented the MIA-induced tissue destruction with a dose-dependent fashion in both cartilage and subchondral bone tissues. The articular knee joints of rats in MIA + D, as the positive control group, also slowed down the tissue destruction inflicted by MIA injection.

Histopathological Evaluation

In histopathological assessment with H&E staining, the tibial plateau of cartilage surface in the sham group was observed as intact and smooth with a well-stained extracellular matrix (Fig. 3A). Histopathological degeneration was observed in MIA + V group such as rough and irregular cartilage surface, decreased staining density and reduced number of chondrocytes owing to severe osteonecrosis (Fig. 3A). UII treatment prevented the histopathological decay in articular cartilage (Fig. 3A). The toluidine blue and safranin O and fast green FCF stainings clearly expressed an improvement regarding the concentration of glycosaminoglycan (Fig. 3B) and proteoglycan (Fig. 3B, C) in the UII-treated groups compared to the MIA + V group. In OA models, the Mankin scoring system was often used in scoring and classification of histopathological lesions based on staining, structural, and cellular alterations in the articular cartilage (Table 1) (Mankin 1971). Total Mankin

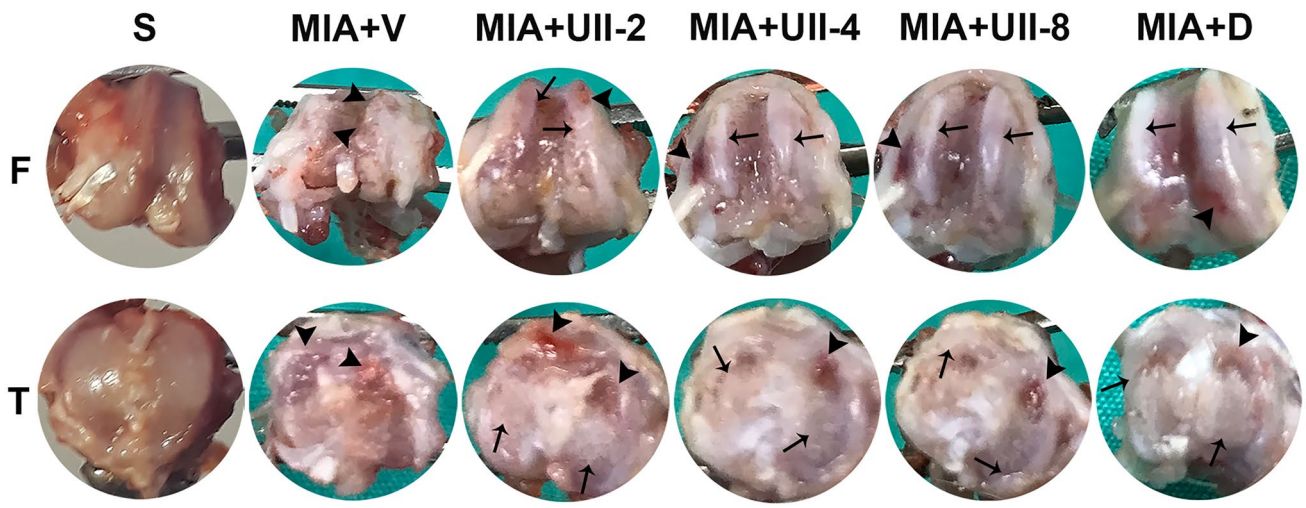


Fig. 2 Gross morphology of knee joint surfaces; femoral condyles (**F**) and tibial plateaus (**T**). Arrowheads indicate the MIA-induced degenerations in cartilage and subchondral bone tissues, whereas arrows point the improved tissue parts after UII or D treatments. *S* Sham, *MIA* Monosodium iodoacetate, *V* Vehicle, *UII-2,4,8* Urotensin-II-2,4,8 µg, *D* Diclofenac

score and the scores at structure, staining, and cells levels increased in the MIA + V group compared to the sham group indicating the substantial cartilage destruction after MIA injection (Fig. 3D–G, $p < 0.05$). UII administrations led to a significant reduction in total Mankin scores of MIA + UII-4 and MIA + UII-8 groups compared to the MIA + V group (Fig. 3A, $p < 0.05$). Regarding individual scores, while UII-4 and UII-8 significantly reduced the structure and cells scores (Fig. 3F, G, $p < 0.05$), just UII-8 led to significant reduction in staining score compared to the MIA + V group (Fig. 3E, $p < 0.05$). All scores decreased in MIA + D positive control compared to MIA + V group (Fig. 3D–G, $p < 0.05$).

Immunohistochemical Findings

The effect of UII treatment on the immunohistochemical expressions of BMP-2, NF-κB, and UII was depicted in Fig. 4. The increased immunohistochemical NF-κB expression was observed in MIA + V group compared to the sham group (Fig. 4A, D, $p < 0.05$). Treatment of UII led to a significant decrease in NF-κB expression in MIA + UII-4 and MIA + UII-8 groups compared to MIA + V group (Fig. 4A, D, $p < 0.05$).

The optical intensity of BMP-2 significantly increased in MIA + V group compared to the sham group (Fig. 4B, E, $p < 0.05$). The expression of BMP-2 significantly decreased in MIA + UII-2, MIA + UII-4, and MIA + UII-8 groups compared to the MIA + V group (Fig. 4B, E, $p < 0.05$). Diclofenac treatment significantly reduced both NF-κB and BMP-2 immunoreactivities compared to MIA + UII-8 group (Fig. 4, $p < 0.05$).

We also performed UII immunohistochemical staining to find out the expression status of UII within articular tissue. We showed that UII is naturally expressed in healthy articular tissue of rats (Fig. 4C). Intra-articular UII expression significantly decreased in MIA + V group compared to the sham group (Fig. 4C, F, $p < 0.05$). We also demonstrated the dose-dependent elevation of intrinsic UII expression after exogenous UII and diclofenac treatments compared to the MIA + V group (Fig. 4C, F, $p < 0.05$).

Correlation Between Histological Lesion Rate and Tissue-Specific BMP-2, NF-κB, and UII Expressions

BMP-2 is known to be upregulated in osteoarthric cartilage and responsible for aggrecan degradation and OA progression through close connection with other destructive enzymes (van der Kraan et al. 2010; Liu et al. 2015a, b). In order to analyze any association between the histological recovery rates and the expression levels of BMP-2, NF-κB, and UII in osteoarthritic cartilage after UII treatment, we performed Spearman's correlation test. We found significant correlations between the total Mankin scores and the staining intensities of NF-κB ($r = 0.8847$, $p < 0.0001$), BMP-2 ($r = 0.9013$, $p < 0.0001$), and UII ($r = -0.9153$, $p < 0.0001$) expressions in articular tissues of the rats (Fig. 5).

Steady Levels of Serum Markers After MIA and UII Treatments

We analyzed the OA-related inflammatory cytokines IL-1β and IL-6 levels together with COMP, as a prominent

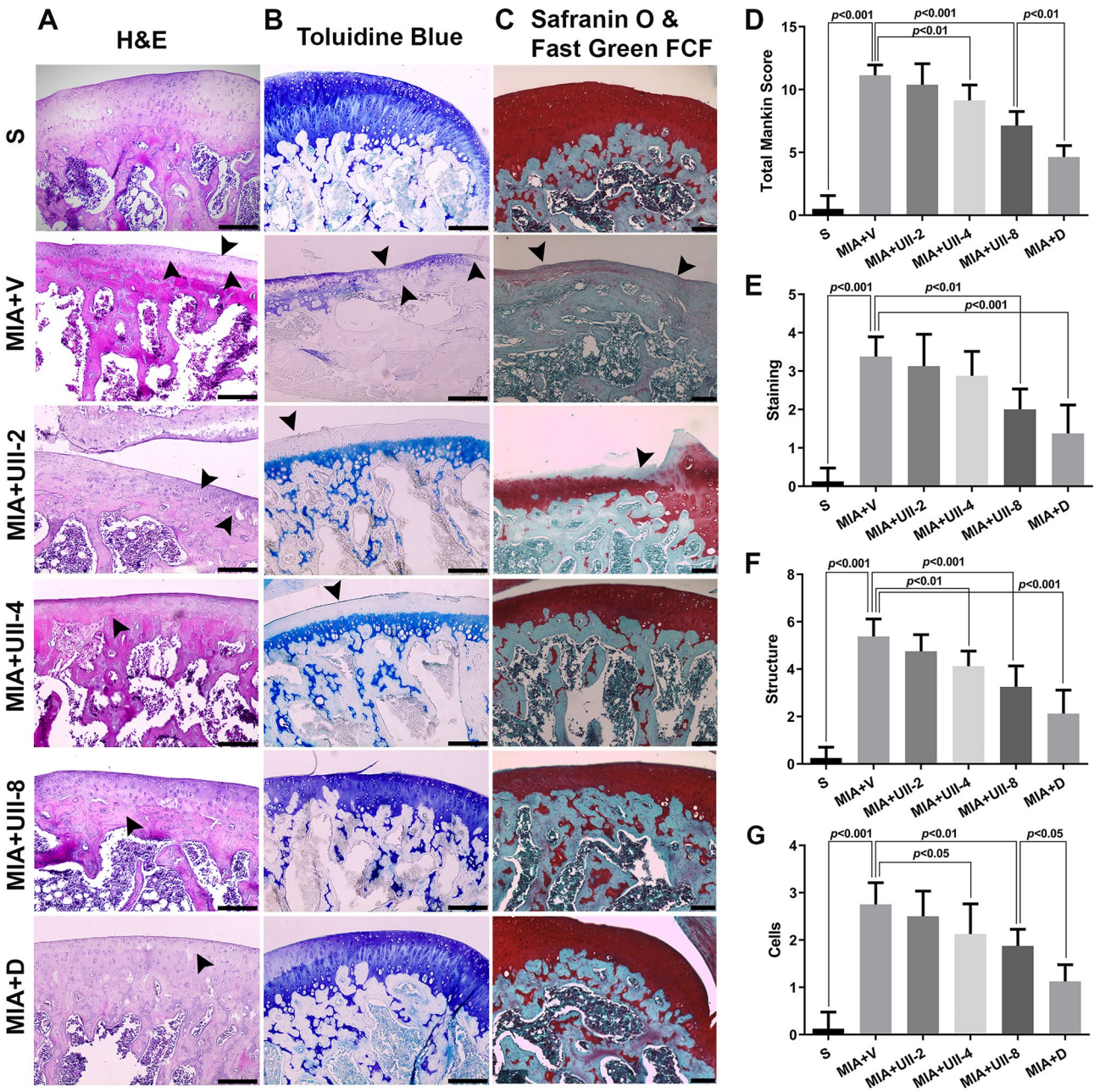


Fig. 3 Effects of UII and diclofenac on articular cartilage histomorphology. Glycosaminoglycan and proteoglycan concentration in the OA rat model depicted with **A** H&E, **B** Toluidine blue, and **C** Safranin O & Fast Green FCF in S, MIA + V, MIA + UII-2,4,8, and MIA + D groups. Based on Mankin score grading system, plots are indicating osteoarthritic cartilage degeneration rates as **D** total Mankin score, and at **E** structure, **F** staining, and **G** cells levels separately in S, MIA + V, MIA + UII-2,4,8, and MIA + D groups. Arrowheads point the regions with decreased cellularity in Safranin O & Fast Green FCF staining. Data were shown as mean ± SD, $n = 8$ per group. Connected lines over bars depict significant p values between groups. Scale bar = 200 µm. *H&E* Hematoxylin and eosine, *S* Sham, *MIA* Monosodium iodoacetate, *V* Vehicle, *UII-2,4,8* Urotensin-II-2,4,8 µg, *D* Diclofenac

biomarker in bone/cartilage pathophysiology, in the sera of osteoarthritic rats with ELISA (Shinmei et al. 1989; Kaneko et al. 2000; Braza-Boils et al. 2012; Hao et al. 2019). We found no significant alterations in the serum levels of these markers in MIA + V group compared to the sham group (Table 2, $p > 0.05$). Besides, UII or diclofenac treatments did not cause any significant change in the levels of analyzed serum markers compared to the MIA + V or sham groups (Table 2, $p > 0.05$).

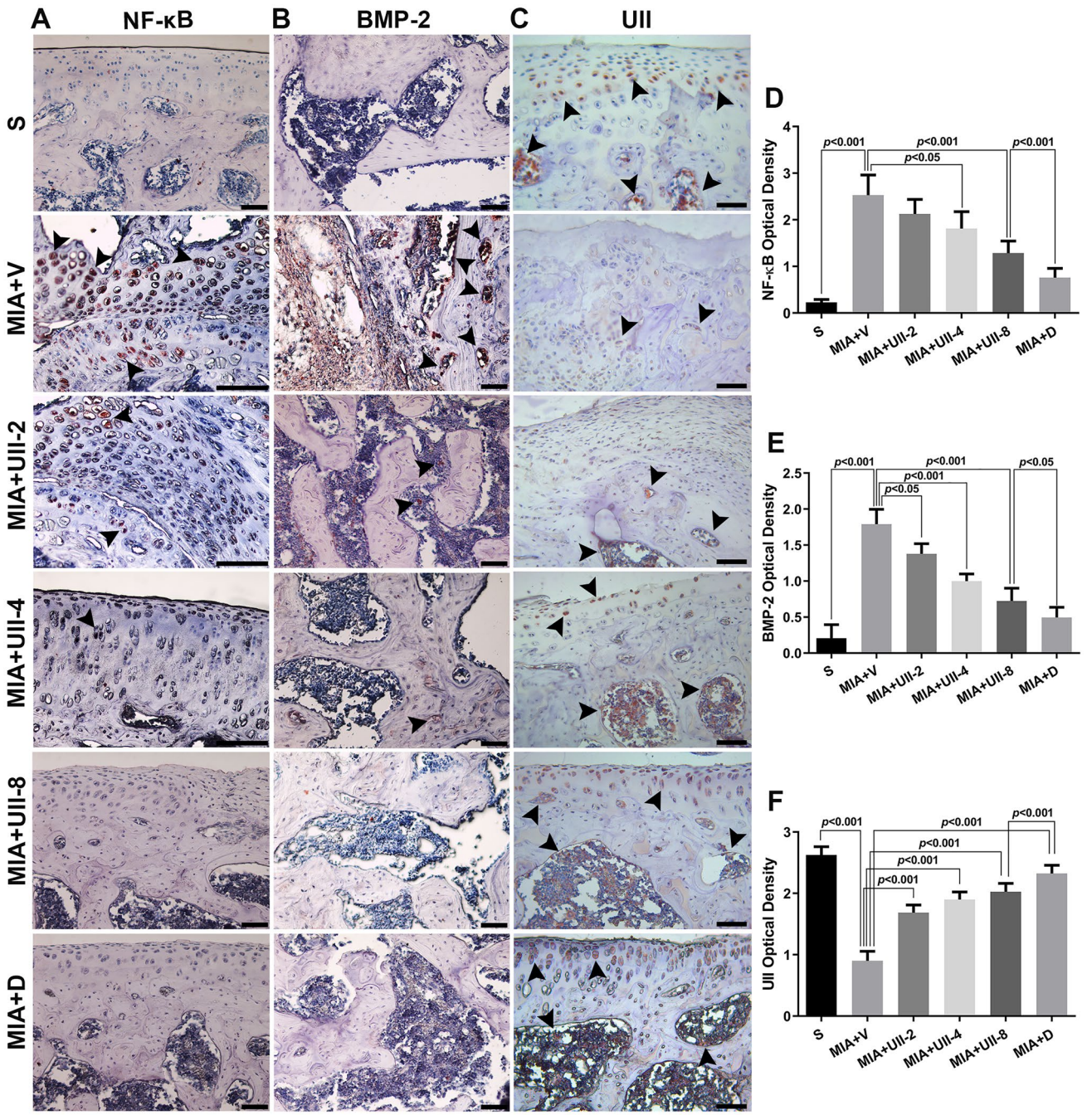


Fig. 4 Effects of UII and diclofenac on the immunohistochemical expression of the relevant biomarkers in MIA-induced OA model in rats. Representative images of **A** NF-κB, **B** BMP-2, **C** UII stainings and **D**, **E**, **F** their corresponding expression levels (optical density) in S, MIA + V, MIA + UII-2,4,8, and MIA + D groups. Positive signals were pointed with arrowheads. Scale bar = 100 µm. Data were shown as mean ± SD, $n = 8$ per group. Connected lines over bars depict significant p values between groups. *NF-κB* Nuclear factor kappa B subunit 1, *BMP-2* Bone morphogenetic protein 2, *UII* Urotensin 2, *S* Sham, *MIA* Monosodium iodoacetate, *V* Vehicle, *UII-2,4,8* Urotensin-II-2,4,8 µg, *D* Diclofenac

Discussion

OA is a pathologic condition emerging as a result of trauma and/or aging along with several other contributory factors such as obesity, mechanical stress, and biochemical and genetic effects (Martel-Pelletier 2004; Felson 2006). The current available therapeutic options, including surgical interventions, are mainly based on the alleviation of the pain but do not provide a full recovery of the impaired joint (Cutolo et al. 2015). The conventional medications utilized

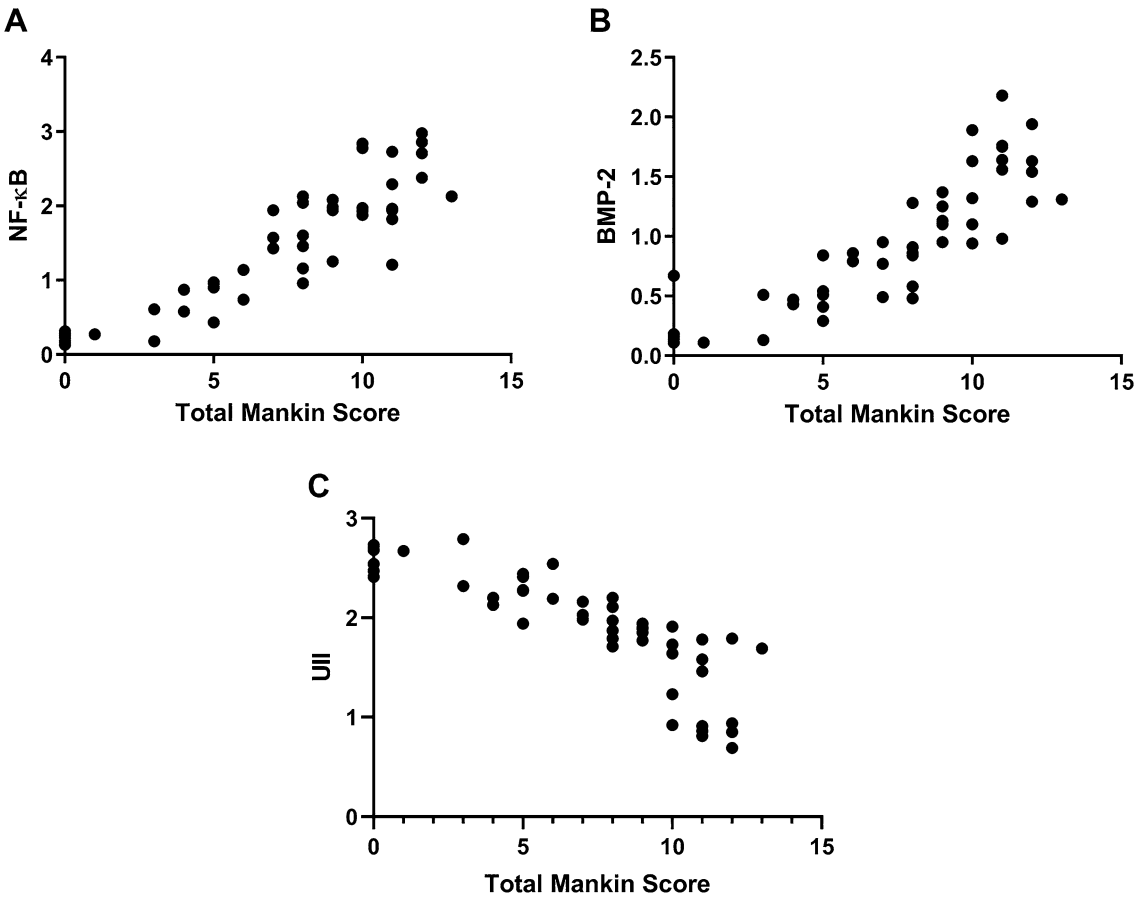


Fig. 5 Spearman's correlation analyses of total Mankin's scores with **A** NF-κB ($r=0.8847$, $p<0.05$), **B** BMP-2 ($r=0.9013$, $P<0.05$) and **C** UII ($r=-0.9153$, $p<0.0001$) levels in osteoarthritic joint tissues. *NF-κB* Nuclear factor kappa B subunit 1, *BMP-2* Bone morphogenetic protein 2, *UII* Urotensin 2

Table 2 The effect of UII administration on serum COMP, IL-6, and IL-1β levels in experimental groups

Serum Parameters	S	MIA + V	MIA + UII-2	MIA + UII-4	MIA + UII-8	MIA + D	*p* value
COMP (ng/ml)	102.3 ± 6.6	93.6 ± 25.2	93.7 ± 24.8	95.0 ± 7.7	71.3 ± 21.6	95.4 ± 10.3	***/**/*** > 0.05**
IL-6 (pg/ml)	64.3 ± 29.7	136.4 ± 160.3	46.6 ± 11.5	144.2 ± 169.8	187.0 ± 218.0	78.7 ± 58.1	***/**/*** > 0.05**
IL-1β (ng/ml)	71.3 ± 26.1	75.4 ± 31.3	42.4 ± 9.1	56.4 ± 16.1	65.9 ± 29.1	51.7 ± 5.7	***/**/*** > 0.05**

Data were represented as the mean ± SD

$p > 0.05$ designates no statistical significance

*Comparison among all groups

**Comparison between MIA + V and sham groups

***Comparison between MIA + V and MIA + UII groups

COMP Cartilage oligomeric matrix protein, *IL-6* Interleukin 6, *IL-1β* Interleukin 1 beta. *S* sham, *MIA* Monosodium iodoacetate, *V* Vehicle, *UII-2,4,8* Urotensin-II-2,4,8 μg, *D* Diclofenac

in the treatment of OA can bring about serious adverse effects such as gastrointestinal tract damage and cardiovascular disorders caused by non-steroidal anti-inflammatory drugs; and cartilage damage caused by intra-articular corticosteroid injection therapies (Coxib et al. 2013; McAlindon et al. 2017). Therefore, it is required to develop novel therapeutic drugs or strategies for long-lasting treatment of OA with minimal side effects. Thus, in the present study we sought to demonstrate the protective effects of intra-articular injection of UII on the osteoarthritic knee joint of rats. We

report for the first time that UII exerted distinct therapeutic impacts on the degenerated knee joint of rats with chemically-induced OA. We demonstrated that intra-articular UII administration significantly prevented cartilage destruction via upregulating intrinsic UII expression and downregulating NF-κB and BMP-2 expressions in the articular joint of osteoarthritic rats.

The studies until now have focused on the unknown onset reasons of OA and on the effective therapeutic options. In the clinical stage of the OA, the patients commonly bear inflammatory reactions ensuing synovitis which is claimed to be the primary cause of the matrix degeneration and OA (Martel-Pelletier 2004). What we know today about the pathophysiology of OA is the implication of the pro-inflammatory cytokines in articular cartilage destruction (Kim et al. 2018). The first clear histopathological symptom of the OA is diminishing of the articular collagen and proteoglycan structures due to activated pro-inflammatory cytokines which eventually leads to degradation of synovial matrix via several matrix metalloproteases and aggrecanases (Tortorella et al. 1999; Braza-Boils et al. 2012). In a MIA-induced OA rat model, the cartilage degeneration was observed related to the time-dependent loss of proteoglycan anabolism, increased gelatinase activity, and IL-1β-mediated inflammatory response in articular regions (Dumond et al. 2004). The previous clinical findings support the claim that elevated cytokine levels such as IL-1β, TNF-α, and IL-6 can cause inflammation-induced cartilage degeneration in OA patients (Shinmei et al. 1989; Dumond et al. 2004). Supporting this, the SF levels of inflammatory cytokines such as IL-1β, IL-6, IL-8, etc. significantly increased in OA patients (Kim et al. 2018). In our study, we did not find any significant alteration in the serum levels of COMP, IL-6, and IL-1β in OA-induced rats. A study conducted with the spontaneous OA model of mice indicated that OA onset and progression did not affect serum levels of IL-1β, TNF-α, and COMP (Braza-Boils et al. 2012). This finding is in line with the steady IL-1β, IL-6, and COMP levels after OA induction in our study. It may be partially due to the fact that the alterations in articular OA-related biomarkers are not always correlated with their corresponding systemic serum levels (Kaneko et al. 2000).

As aforementioned above, UII is a short cyclic vasoactive peptide with a known expression pattern in several tissues of the human body except knee joints (Pearson et al. 1980). After immunohistochemical analyses, our group was to be the first to demonstrate the articular expression pattern of UII in knee joints of the rats. Firstly, MIA-induction significantly lowered the UII expression in osteoarthritic tissue of the rats compared to the sham group. After UII treatment, we found a significant increase in articular UII expression in a dose-dependent manner. It was claimed that there is a close connection between UII expression and the inflammatory reactions in onset or progression of several diseases (Gogebakan et al. 2014; Sun and Liu 2019). In our OA model, however, we found that intra-articular UII injection incited the intrinsic expression of UII. Furthermore, there was a strong negative correlation between articular UII expression and tissue degeneration level. It can be inferred from our findings that the restoration of intrinsic UII expression after extrinsic UII administration in the articular region prevented the further MIA-induced destruction of cartilage tissue in the rats.

Several signaling pathways have been shown to be implicated in the pathogenesis of OA including NF-κB (Kim et al. 2018). NF-κB acts as a central molecule in promoting inflammation-induced cartilage degeneration in OA by igniting the inflammatory cytokines, which can re-stimulate NF-κB in a positive feedback manner (Rigoglou and Papavassiliou 2013). The NF-κB pathway was also implicated in chondrocyte apoptosis in an IL-1β-induced cell line model (Pan et al. 2018). Supporting the idea, it was demonstrated that the knock-down of NF-κB ameliorated the cartilage breakdown in a surgical rat model of OA (Chen et al. 2008). Along with the previous findings, we showed the downregulation of NF-κB expression in knee joint after UII treatment that contributed to the slowdown of the osteoarthritic knee joint degeneration. On the other hand, the blockade of UII/UTR via its specific antagonist was previously shown to attenuate the NF-κB-activated inflammatory reactions in in vivo and in vitro inflammatory-disease models (Liang et al. 2014; Liu et al. 2015a, b). Another in vivo sepsis-induced lung injury animal model demonstrated the upregulation of NF-κB levels after intraperitoneal UII administration (Ugan et al. 2018). Our results seem to be contradicting with these findings; however, we administered exogeneous UII peptide locally in our model rather than systemic injection or intrinsic manipulation of UII expression and/or UII/UTR pathway via specific inhibitors. Our strategy could likely interfere and distort the intrinsic action mechanism of UII/URT pathway owing to the paracrine and autocrine natures of UII activity over intra- and extra-cellular regions (Castel et al. 2017). As aforementioned, several pathways are implicated in OA progression like apoptosis. In an in vitro oxidative stress cardiomyocyte cell line model, UII treatment reduced apoptosis via ERK upregulation (Gong et al. 2015) which presumably down modulated the NF-κB-induced apoptosis (Shi et al. 2015). In our model, the downregulation of NF-κB post-UII treatment can be implied as the protection of articular cells from apoptosis induced by OA.

NF-κB pathway is mostly triggered together with other pathways including BMP to inhibit chondrogenesis and activate other matrix-degrading enzymes (Lepetsos et al. 2019). Several lines of evidence revealed that BMP pathway-related proteins can play a central role in the formation of hypertrophic chondrocytes that causes matrix degeneration during

OA pathogenesis via upregulation of matrix metalloproteinases (van der Kraan et al. 2010; Brescia et al. 2014). Moreover, it was demonstrated that NF-κB could also stimulate the upregulation of BMP-2 in hypertrophic chondrocytes in a transgenic mouse model (Ijiri et al. 2005). The upregulation of BMP-2 expression at gene levels was also shown in an exercise-induced OA rat model (Liu et al. 2016). On the one hand, the anabolic and chondroprotective effects of BMP family proteins are also known (Liu et al. 2015a, b); thus the significant upregulation of BMP-2 within the osteoarthritic cartilage region in our model can also be an endogenous chondroprotective response to cartilage degeneration. On the other hand, articular BMP-2 administration has been previously demonstrated to cause osteophytes in the ectopic regions of murine knee cartilage (Scharstuhl et al. 2003). We also demonstrated the significant reduction in BMP-2 expression ensuing tissue recovery concurrently in UII-treated tissues, which clearly exhibits the involvement of BMP-2 and UII in articular tissue physiology. In line with our data, the central role of the BMP-2 pathway has been shown in both in vitro and in vivo models of OA by suggesting that IL-1β increased BMP-2 expression and blocking of BMP-2 via its inhibitors improved the degenerated cartilage tissue in knee joints of rats with OA (Chien et al. 2020). It was also previously suggested that transforming growth factor-beta 1/BMP signaling pathways are of critical importance for the maintenance of cartilage homeostasis, and any disturbance of this balance in favor of BMP can result in cartilage chondrocyte loss (Shen et al. 2017). Moreover, we have found significant positive correlations between histopathological lesion rate and tissue-specific expressions of NF-κB and BMP-2 pointing out the fact that both proteins are valid markers in assessing cartilage degeneration.

As to the best our knowledge, we are the first group investigating the effect of articular UII treatment on the pathogenesis of our MIA-induced OA model in rats. We demonstrated that UII treatment significantly restrained the MIA-induced articular tissue degeneration and partially protected the cartilage and subchondral bone as depicted in gross morphology and histological and immunohistochemical analyses (Figs. 2, 3, 4). In previous studies, UII has been linked to the pathogeneses of several diseases with respect to inflammatory responses (McDonald et al. 2007). A clinical study conducted with OA and non-OA patients suggested that the elevated levels of UII in the SF of the OA patients can be related to the synovial fibrosis during OA progression (Gogebakan et al. 2014). It has been also reported decades ago that UII acts as an osmoregulator to establish the hemostasis of the body fluids not only in fishes but also in vertebrates, including humans (Balment et al. 2005). The SF is produced by ultrafiltration from blood plasma by synovial cells. Considering the fact that the deterioration of the SF quality and quantity during OA pathogenesis (More et al. 2020; Seidman and Limaiem 2020), we can assume that the elevation of endogenous synovial UII expression in the patients with knee OA can be a protective response against cartilage destruction due to the reduced SF in both quality and quantity. Supporting this idea, a previous study demonstrated the expression of UII receptor in the chondrocytes within hyaline cartilage of amphibians and rats and presumed a modulatory role of UII in cartilage matrix remodeling (Konno et al. 2013).

Last but not least, in our study, the exogenous intra-articular UII administration could prevent the inflammation-induced destruction of articular matrix composition presumably by interfering the endogenous UII/UTR pathway regulated by autocrine and paracrine mechanisms as ascertained previously (Castel et al. 2017). However, the protective effect of UII in the present model can be context-specific, meaning that extrinsic UII can act differently in other in vivo systems e.g., surgical or age-induced OA models.

Conclusions

Based on our findings, the external UII treatment could slow down cartilage degeneration and help to prevent the cartilage tissue damage through downregulation of NF-κB and BMP-2 proteins and compensation of the intrinsic UII expression via inducing its upregulation. Since UII is a strong vasoactive peptide, it can be speculated that the restored intrinsic UII expression in the joint tissue may reconstitute the rheological characteristics of the synovial fluid load. To the best of our knowledge, there are no studies in the literature analyzing the effect of exogenous UII administration on the knee joint of MIA-induced osteoarthritic rats. To elucidate the underlying action mechanism of UII on knee joint pathophysiology during OA, further experiments are warranted.

Acknowledgements None

Author Contributions MYT and HMO designed the study. MYT, HMO, and İK: Wrote the manuscript and all authors drafted/edited it and interpreted the results. MYT, HMO, İK, CEG, DT, and AK: performed experiments and laboratory analyses. MYT, HMO, and İK: conducted analyses, prepared tables/graphs/figures and all authors revised the manuscript.

Funding The authors declare no specific funding for this work.

Declarations

Conflict of interest There are no conflicting interests.

Ethical Approval The ethical approval was acquired for this study from the "Animal Ethics Committee of Hatay Mustafa Kemal University" (2020/4–18).

References

Balment RJ, Song W, Ashton N (2005) Urotensin II: ancient hormone with new functions in vertebrate body fluid regulation. Ann N Y Acad Sci 1040:66–73. https://doi.org/10.1196/annals.1327.007

Bove SE, Calcaterra SL, Brooker RM, Huber CM, Guzman RE, Juneau PL, Schrier DJ, Kilgore KS (2003) Weight bearing as a measure of disease progression and efficacy of anti-inflammatory compounds in a model of monosodium iodoacetate-induced osteoarthritis. Osteoarthr Cartil 11:821–830

Braza-Boils A, Ferrandiz ML, Terencio MC, Alcaraz MJ (2012) Analysis of early biochemical markers and regulation by tin protoporphyrin IX in a model of spontaneous osteoarthritis. Exp Gerontol 47:406–409. https://doi.org/10.1016/j.exger.2012.03.005

Brescia AC, Simonds MM, McCahan SM, Fawcett PT, Rose CD (2014) The role of transforming growth factor beta signaling in fibroblast-like synoviocytes from patients with oligoarticular juvenile idiopathic arthritis: dysregulation of transforming growth factor beta signaling, including overexpression of bone morphogenetic protein 4, may lead to a chondrocyte phenotype and may contribute to bony hypertrophy. Arthritis Rheumatol 66:1352–1362. https://doi.org/10.1002/art.38336

Cao P, Li Y, Tang Y, Ding C, Hunter DJ (2020) Pharmacotherapy for knee osteoarthritis: current and emerging therapies. Expert Opin Pharmacother 21:797–809. https://doi.org/10.1080/14656566.2020.1732924

Castel H, Desrues L, Joubert JE, Tonon MC, Prezeau L, Chabbert M, Morin F, Gandolfo P (2017) The G protein-coupled receptor UT of the neuropeptide urotensin II displays structural and functional chemokine features. Front Endocrinol (lausanne) 8:76. https://doi.org/10.3389/fendo.2017.00076

Chen LX, Lin L, Wang HJ, Wei XL, Fu X, Zhang JY, Yu CL (2008) Suppression of early experimental osteoarthritis by in vivo delivery of the adenoviral vector-mediated NF-kappaBp65-specific siRNA. Osteoarthr Cartil 16:174–184. https://doi.org/10.1016/j.joca.2007.06.006

Chen YL, Loh SH, Chen JJ, Tsai CS (2012) Urotensin II prevents cardiomyocyte apoptosis induced by doxorubicin via Akt and ERK. Eur J Pharmacol 680:88–94. https://doi.org/10.1016/j.ejphar.2012.01.034

Chen YL, Tsai YT, Lee CY, Lee CH, Chen CY, Liu CM, Chen JJ, Loh SH, Tsai CS (2014) Urotensin II inhibits doxorubicin-induced human umbilical vein endothelial cell death by modulating ATF expression and via the ERK and Akt pathway. PLoS ONE 9:e106812. https://doi.org/10.1371/journal.pone.0106812

Chien SY, Tsai CH, Liu SC, Huang CC, Lin TH, Yang YZ, Tang CH (2020) Noggin inhibits IL-1beta and BMP-2 expression, and attenuates cartilage degeneration and subchondral bone destruction in experimental osteoarthritis. Cells. https://doi.org/10.3390/cells9040927

Coxib, NTC traditional, Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C (2013) Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 382:769–779. https://doi.org/10.1016/S0140-6736(13)60900-9

Cutolo M, Berenbaum F, Hochberg M, Punzi L, Reginster JY (2015) Commentary on recent therapeutic guidelines for osteoarthritis. Semin Arthritis Rheum 44:611–617. https://doi.org/10.1016/j.semarthrit.2014.12.003

Disease GBD, Injury I, Prevalence C (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Dumond H, Presle N, Pottie P, Pacquelet S, Terlain B, Netter P, Gepstein A, Livne E, Jouzeau JY (2004) Site specific changes in gene expression and cartilage metabolism during early experimental osteoarthritis. Osteoarthr Cartil 12:284–295. https://doi.org/10.1016/j.joca.2003.11.008

Felson DT (2006) Clinical practice. Osteoarthritis of the knee. N Engl J Med 354:841–848. https://doi.org/10.1056/NEJMcp051726

Geyer M, Schonfeld C (2018) Novel insights into the pathogenesis of osteoarthritis. Curr Rheumatol Rev 14:98–107. https://doi.org/10.2174/1573397113666170807122312

Gogebakan B, Uruc V, Ozden R, Duman IG, Yagiz AE, Okuyan HM, Aldemir O, Dogramaci Y, Kalaci A (2014) Urotensin II (U-II), a novel cyclic peptide, possibly associated with the pathophysiology of osteoarthritis. Peptides 54:159–161. https://doi.org/10.1016/j.peptides.2014.01.010

Goldring MB, Marcu KB (2009) Cartilage homeostasis in health and rheumatic diseases. Arthritis Res Ther 11:224. https://doi.org/10.1186/ar2592

Gong H, Chen Z, Zhang X, Li Y, Zhang J, Chen Y, Ding Y, Zhang G, Yang C, Zhu Y, Zou Y (2015) Urotensin II protects cardiomyocytes from apoptosis induced by oxidative stress through the CSE/H2S pathway. Int J Mol Sci 16:12482–12498. https://doi.org/10.3390/ijms160612482

Guzman RE, Evans MG, Bove S, Morenko B, Kilgore K (2003) Mono-iodoacetate-induced histologic changes in subchondral bone and articular cartilage of rat femorotibial joints: an animal model of osteoarthritis. Toxicol Pathol 31:619–624. https://doi.org/10.1080/01926230390241800

Hao HQ, Zhang JF, He QQ, Wang Z (2019) Cartilage oligomeric matrix protein, C-terminal cross-linking telopeptide of type II collagen, and matrix metalloproteinase-3 as biomarkers for knee and hip osteoarthritis (OA) diagnosis: a systematic review and meta-analysis. Osteoarthr Cartil 27:726–736. https://doi.org/10.1016/j.joca.2018.10.009

Hsu YH, Chen TH, Chen YC, Cheng CY, Sue YM, Chen JR, Chen CH (2013) Urotensin II exerts antiapoptotic effect on NRK-52E cells through prostacyclin-mediated peroxisome proliferator-activated receptor alpha and Akt activation. Mol Cell Endocrinol 381:168–174. https://doi.org/10.1016/j.mce.2013.07.028

Ijiri K, Zerbini LF, Peng H, Correa RG, Lu B, Walsh N, Zhao Y, Taniguchi N, Huang XL, Otu H, Wang H, Wang JF, Komiya S, Ducy P, Rahman MU, Flavell RA, Gravallese EM, Oettgen P, Libermann TA, Goldring MB (2005) A novel role for GADD-45beta as a mediator of MMP-13 gene expression during chondrocyte terminal differentiation. J Biol Chem 280:38544–38555. https://doi.org/10.1074/jbc.M504202200

Kaneko S, Satoh T, Chiba J, Ju C, Inoue K, Kagawa J (2000) Interleukin-6 and interleukin-8 levels in serum and synovial fluid of patients with osteoarthritis. Cytokines Cell Mol Ther 6:71–79

Kemp W, Kompa A, Phrommintikul A, Herath C, Zhiyuan J, Angus P, McLean C, Roberts S, Krum H (2009) Urotensin II modulates hepatic fibrosis and portal hemodynamic alterations in rats. Am

J Physiol Gastrointest Liver Physiol 297:G762-767. https://doi.org/10.1152/ajpgi.00127.2009
Kim WK, Chung HJ, Pyee Y, Choi TJ, Park HJ, Hong JY, Shin JS, Lee JH, Ha IH, Lee SK (2016) Effects of intra-articular SHINBARO treatment on monosodium iodoacetate-induced osteoarthritis in rats. Chin Med 11:17. https://doi.org/10.1186/s13020-016-0089-6
Kim JR, Yoo JJ, Kim HA (2018) Therapeutics in osteoarthritis based on an understanding of its molecular pathogenesis. Int J Mol Sci. https://doi.org/10.3390/ijms19030674
Konno N, Fujii Y, Imae H, Kaiya H, Mukuda T, Miyazato M, Matsuda K, Uchiyama M (2013) Urotensin II receptor (UTR) exists in hyaline chondrocytes: a study of peripheral distribution of UTR in the African clawed frog, Xenopus laevis. Gen Comp Endocrinol 185:44–56. https://doi.org/10.1016/j.ygcen.2013.01.015
Kuyinu EL, Narayanan G, Nair LS, Laurencin CT (2016) Animal models of osteoarthritis: classification, update, and measurement of outcomes. J Orthop Surg Res 11:19. https://doi.org/10.1186/s13018-016-0346-5
Lepetsos P, Papavassiliou KA, Papavassiliou AG (2019) Redox and NF-kappaB signaling in osteoarthritis. Free Radic Biol Med 132:90–100. https://doi.org/10.1016/j.freeradbiomed.2018.09.025
Liang DY, Liu LM, Ye CG, Zhao L, Yu FP, Gao DY, Wang YY, Yang ZW, Wang YY (2014) Inhibition of UII/UTR system relieves acute inflammation of liver through preventing activation of NF-kappaB pathway in ALF mice. PLoS ONE 8:e64895. https://doi.org/10.1371/journal.pone.0064895
Liu LM, Liang DY, Ye CG, Tu WJ, Zhu T (2015a) The UII/UT system mediates upregulation of proinflammatory cytokines through p38 MAPK and NF-kappaB pathways in LPS-stimulated Kupffer cells. PLoS ONE 10:e0121383. https://doi.org/10.1371/journal.pone.0121383
Liu Y, Hou R, Yin R, Yin W (2015b) Correlation of bone morphogenetic protein-2 levels in serum and synovial fluid with disease severity of knee osteoarthritis. Med Sci Monit 21:363–370. https://doi.org/10.12659/MSM.892160
Liu SS, Zhou P, Zhang Y (2016) Abnormal expression of key genes and proteins in the canonical Wnt/beta-catenin pathway of articular cartilage in a rat model of exercise-induced osteoarthritis. Mol Med Rep 13:1999–2006. https://doi.org/10.3892/mmr.2016.4798
Lu J, Zhang T, Sun H, Wang S, Liu M (2018) Protective effects of dioscin against cartilage destruction in a monosodium iodoacetate (MIA)-indcued osteoarthritis rat model. Biomed Pharmacother 108:1029–1038
Lunenfeld B, Stratton P (2013) The clinical consequences of an ageing world and preventive strategies. Best Pract Res Clin Obstet Gynaecol 27:643–659. https://doi.org/10.1016/j.bpobgyn.2013.02.005
Mankin H, Dorfman H, Lippiello L, Zarins A (1971) Biochemical and metabolic abnormalities in articular cartilage from osteo-arthritic human hips: II correlation of morphology with biochemical and metabolic data. J Bone Joint Surg 53:523–537
Martel-Pelletier J (2004) Pathophysiology of osteoarthritis. Osteoarthr Cartil 12:S31-33. https://doi.org/10.1016/j.joca.2003.10.002
McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, Ward RJ (2017) Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 317:1967–1975. https://doi.org/10.1001/jama.2017.5283
McDonald J, Batuwangala M, Lambert DG (2007) Role of urotensin II and its receptor in health and disease. J Anesth 21:378–389. https://doi.org/10.1007/s00540-007-0524-z
Mobasheri A, Batt M (2016) An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med 59:333–339. https://doi.org/10.1016/j.rehab.2016.07.004
More S, Kotiya A, Kotia A, Ghosh SK, Spyrou LA, Sarris IE (2020) Rheological properties of synovial fluid due to viscosupplements: a review for osteoarthritis remedy. Comput Methods Programs Biomed 196:105644. https://doi.org/10.1016/j.cmpb.2020.105644
Okuyan HM, Terzi MY, Karaboga I, Dogan S, Kalaci A (2020) In vivo protective effects of upper zone of growth plate and cartilage matrix associated protein against cartilage degeneration in a monosodium iodoacetate induced osteoarthritis model. Can J Physiol Pharmacol 98:763–770. https://doi.org/10.1139/cjpp-2020-0009
Okuyan HM, Terzi MY, Duran G, Kalaci A (2021) The role of urotensin II associated with inflammation in human osteoblast cells. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksek Okulu Dergisi 9:353–361
Onat AM, Turkbeyler IH, Pehlivan Y, Demir T, Kaplan DS, Taysi S, Ceribasi AO, Tutar E, Kisacik B (2012) The efficiency of a urotensin II antagonist in an experimental lung fibrosis model. Inflammation 35:1138–1143. https://doi.org/10.1007/s10753-011-9421-6
Pan T, Shi X, Chen H, Chen R, Wu D, Lin Z, Zhang J, Pan J (2018) Geniposide suppresses interleukin-1beta-induced inflammation and apoptosis in rat chondrocytes via the PI3K/Akt/NF-kappaB Signaling pathway. Inflammation 41:390–399. https://doi.org/10.1007/s10753-017-0694-2
Pearson D, Shively JE, Clark BR, Geschwind M II, Barkley RSN, Bern HA (1980) Urotensin II: a somatostatin-like peptide in the caudal neurosecretory system of fishes. Proc Natl Acad Sci USA 77:5021–5024. https://doi.org/10.1073/pnas.77.8.5021
Pereira-Castro J, Bras-Silva C, Fontes-Sousa AP (2019) Novel insights into the role of urotensin II in cardiovascular disease. Drug Discov Today 24:2170–2180. https://doi.org/10.1016/j.drudis.2019.08.005
Rigoglou S, Papavassiliou AG (2013) The NF-kappaB signalling pathway in osteoarthritis. Int J Biochem Cell Biol 45:2580–2584. https://doi.org/10.1016/j.biocel.2013.08.018
Ross B, McKendy K, Giaid A (2010) Role of urotensin II in health and disease. Am J Physiol Regul Integr Comp Physiol 298:R1156-1172. https://doi.org/10.1152/ajpregu.00706.2009
Scharstuhl A, Vitters EL, van der Kraan PM, van den Berg WB (2003) Reduction of osteophyte formation and synovial thickening by adenoviral overexpression of transforming growth factor beta/bone morphogenetic protein inhibitors during experimental osteoarthritis. Arthritis Rheum 48:3442–3451. https://doi.org/10.1002/art.11328
Seidman AJ, Limaiem F (2020) Synovial fluid analysis. StatPearls, Treasure Island (FL)
Shen J, Wang C, Li D, Xu T, Myers J, Ashton JM, Wang T, Zuscik MJ, McAlinden A, O'Keefe RJ (2017) DNA methyltransferase 3b regulates articular cartilage homeostasis by altering metabolism. JCI Insight. https://doi.org/10.1172/jci.insight.93612
Shi M, He X, Wei W, Wang J, Zhang T, Shen X (2015) Tenascin-C induces resistance to apoptosis in pancreatic cancer cell through activation of ERK/NF-kappaB pathway. Apoptosis 20:843–857. https://doi.org/10.1007/s10495-015-1106-4
Shinmei M, Masuda K, Kikuchi T, Shimomura Y (1989) Interleukin 1, tumor necrosis factor, and interleukin 6 as mediators of cartilage destruction. Semin Arthritis Rheum 18:27–32. https://doi.org/10.1016/0049-0172(89)90081-4
Sun SL, Liu LM (2019) Urotensin II: an inflammatory cytokine. J Endocrinol. https://doi.org/10.1530/JOE-18-0505
Teeple E, Jay GD, Elsaid KA, Fleming BC (2013) Animal models of osteoarthritis: challenges of model selection and analysis. AAPS J 15:438–446. https://doi.org/10.1208/s12248-013-9454-x
Tortorella MD, Burn TC, Pratta MA, Abbaszade I, Hollis JM, Liu R, Rosenfeld SA, Copeland RA, Decicco CP, Wynn R, Rockwell A, Yang F, Duke JL, Solomon K, George H, Bruckner R, Nagase H, Itoh Y, Ellis DM, Ross H, Wiswall BH, Murphy K, Hillman MC

Jr, Hollis GF, Newton RC, Magolda RL, Trzaskos JM, Arner EC (1999) Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science 284:1664–1666. https://doi.org/10.1126/science.284.5420.1664

Ugan RA, Cadirci E, Halici Z, Toktay E, Cinar I (2018) The role of urotensin-II and its receptors in sepsis-induced lung injury under diabetic conditions. Eur J Pharmacol 818:457–469. https://doi.org/10.1016/j.ejphar.2017.11.011

van der Kraan PM, Blaney Davidson EN, van den Berg WB (2010) Bone morphogenetic proteins and articular cartilage: to serve and protect or a wolf in sheep clothing's? Osteoarthr Cartil 18:735–741. https://doi.org/10.1016/j.joca.2010.03.001

Wu YQ, Song Z, Zhou CH, Xing SH, Pei DS, Zheng JN (2010) Expression of urotensin II and its receptor in human lung adenocarcinoma A549 cells and the effect of urotensin II on lung adenocarcinoma growth in vitro and in vivo. Oncol Rep 24:1179–1184. https://doi.org/10.3892/or_00000970

Yang Y, Zhang J, Chen X, Wu T, Xu X, Cao G, Li H, Li Y (2016) UII/GPR14 is involved in NF-kappaB-mediated colonic inflammation in vivo and in vitro. Oncol Rep 36:2800–2806. https://doi.org/10.3892/or.2016.5069

Zhang YG, Li YG, Liu BG, Wei RH, Wang DM, Tan XR, Bu DF, Pang YZ, Tang CS (2007) Urotensin II accelerates cardiac fibrosis and hypertrophy of rats induced by isoproterenol. Acta Pharmacol Sin 28:36–43. https://doi.org/10.1111/j.1745-7254.2007.00485.x

Authors and Affiliations

Menderes Yusuf Terzi[1,2] · Hamza Malik Okuyan[3] · İhsan Karaboğa[4] · Cemil Emre Gökdemir[5] · Duygu Tap[2] · Aydıner Kalacı[5]

✉ Menderes Yusuf Terzi
menderesyusufterzi@gmail.com; myterzi@mku.edu.tr

[1] Department of Medical Biology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey

[2] Department of Molecular Biochemistry and Genetics, Graduate School of Health Sciences, Hatay Mustafa Kemal University, Hatay, Turkey

[3] Department of Biomedical Engineering, Department of Physiotherapy and Rehabilitation-Faculty of Health Sciences, Sakarya University of Applied Sciences, Sakarya, Turkey

[4] Department of Emergency and Disaster Management, School of Health, Tekirdağ Namık Kemal University, Tekirdağ, Turkey

[5] Department of Orthopedics and Traumatology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey