assessed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). At least three random fields were evaluated for each type of ST, quantifying the expression of INHBA, TNF- α , MMP12 and CD209 in all segmented CD163⁺ macrophages. Macrophages density was normalised based on selected tissue area (mm²). After background subtraction, data were plotted using Graph-Pad software (GraphPad Software, La Jolla, CA, USA).

Results: CD163⁺ sublining (SL) macrophages from UA-RA expressed abundantly the INHBA-encoded activin A, whereas TNF α and MMP12 were variably detected. Regarding the M-CSF-associated marker CD209, 2 populations of CD163⁺ macrophages were found in the SL of UA-RA, CD163⁺CD209⁺ and the other CD163⁺CD209⁻, with higher than 100 arbitrary units (au) for CD163⁺CD209⁺ and lower than 100 au for CD163⁺CD209⁻. Similarly, INHBA, MMP12 and TNF α expression and 2 populations of CD209 were detected in CD163⁺ macrophages from UA-PsA. Macrophage density was also found comparable between UA, with 650/mm² in UA-RA and 649/mm² in UA-PsA. Quantification of the above indicated markers in CD163⁺ST macrophages from established RA and PsA revealed similar levels of INHBA, TNF α , MMP12 and CD209 than those from UA-RA and UA-PsA.

Conclusions: This study shows for the first time that the polarisation state of ST CD163⁺ macrophages in UA progressing to RA and PsA is similar to that of established RA and PsA in terms of INHBA, MMP12, TNF α and CD209 expression. Therefore, the inflammatory polarisation state of macrophages is similar in RA and PsA and it is already detected at the earlier steps.

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AB0089

HISTOPATHOLOGICAL CHANGE CAUSED BY BIOLOGICAL TREATMENT IN RHEUMATOID ARTHRITIS SYNOVIAL TISSUE

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Background: Multiple studies addressing the effects of biologics on the synovial tissue in rheumatoid arthritis (RA) patients have been reported. There are, however, few studies comparing histopathological changes in the synovial tissue in the same RA patients between before and after biologics treatment.

Objectives: We examined biologics impacts on RA synovial tissues based on pathological findings in them collected during surgeries for the same patient before and after biological drug usage.

Methods: Synovial tissues were collected from 34 RA joints before and after biologics. The average age and disease duration of the study subjects were 64.0 and 22.5, respectively. Synovial tissues were evaluated by hematoxylin. Histopathological changes in the synovial tissues were compared based on Rooney's score, and presence or absence of fibrinoid degeneration and proliferation of villi in the subsynovial tissue. We examined correlation between pathological findings in RA synovium and disease activity under biologics. Disease activity was assessed by CDAI. We examined the Histopathological changes in the Remission, Low disease activity group (RL group) and Moderate disease activity (M group). Etanercept, Infliximab, Tocilizumab, Adalimumab and Abatacept was used as biological drug for 18, 6, 5, 3 and 2 joints respectively.

Results: Rooney score between before and after biological usage improved from 28.4 to 12.0 showing significant difference. Significant improvement in Rooney score was observed in all items. Fibrinoid degeneration was observed in 29 cases (85.3%) and 6 cases (17.6%) before and after biologics treatment, respectively, demonstrating a significant reduction with biologics treatment. Proliferation of villi was observed in 32 cases (94.1%) and 11 (32.4%) before and after biologics treatment, respectively, demonstrating a significant reduction with biologics treatment. After biologics treatment, Rooney's score in RL group and M group were 10.4 and 15.3, respectively, showing a statistically significant difference. In addition, the M group had significantly higher scores in lymphoid follicle and lymphocyte infiltration compared to the RL group.

Conclusions: The study results demonstrated that biologics treatment significantly ameliorated inflammatory changes in the synovial lining layers and sublining layers. In addition, the results suggested that histopathological findings in the sublining layers reflected disease activity.

Disclosure of Interest: None declared

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AB0090

VERBASCOSIDE AND HYDROXYTYROSOL DOWNREGULATE STRESS-RELATED PATHWAYS IN HUMAN OSTEOARTHRITIC ARTICULAR CHONDROCYTES

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Background: Osteoarthritis (OA), is a leading cause of joint dysfunction and the disease is characterised by progressive destruction of the articular cartilage.¹ At the molecular level, degeneration of the cartilage is attributed to multifactorial events including oxidative stress, mitochondrial dysfunction, apoptosis and associated changes in inflammatory and catabolic gene expression.² Recent studies have revealed the essential role of plant-derived antioxidants in preventing pathological events observed in joint diseases by modulating redox signalling.³

Objectives: Here, we studied whether the polyphenolic compounds verbascoside and hydroxytyrosol exert chondroprotective effects by suppressing oxidative stress pathways and IL-1, IL-1 β -converting enzyme (ICE) expression in human OA chondrocytes.

Methods: Chondrocytes were isolated from the joint cartilages of OA patients (grade 3–4) during total knee arthroplasty with the approval of Kecioren Training and Research Hospital, Clinical Research Ethics Committee (B.10.4.İSM.4.06.68.49), as described previously.⁴ The alterations in cell counts, viability (MTT, NRU), proliferation (RTCA-iCELLigence System), reactive oxygen species (ROS) generation, stress-related signalling proteins and inflammatory progenitors ICE/caspase-1 (ELISA) were determined.

Results: Cell viability was increased at lower concentrations of hydroxytyrosol in OA chondrocytes (P1, 30th day). On the other hand, verbascoside treated cells did not show any difference in the activity of mitochondrial oxidoreductases by the MTT assay. However, both polyphenols significantly increased proliferation and reduced intracellular ROS generation in OA chondrocytes at lower concentrations. Although verbascoside has no effect on ICE/caspase-1, treatment with hydroxytyrosol downregulated ICE/caspase-1, indicating a potential anti-inflammatory effect. Both polyphenols modulated the activation of stress activated signalling pathways via p38 and JNK proteins.

Conclusions: At low concentrations the antioxidants hydroxytyrosol and verbascoside may have potential chondroprotective effects in OA.

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AB0091

MECHANICAL EXPOSURE AND DIACEREIN TREATMENT MODULATES INTEGRIN-FAK-MAPKS MECHANOTRANSDUCTION IN HUMAN OSTEOARTHRITIS CHONDROCYTES

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Background: Progression of osteoarthritis (OA) is characterised by destruction of articular cartilage, thickening of subchondral bone, and formation of osteophytes. The disease modifying OA drug (DMOAD) diacerein functions as a slow acting drug through anti-inflammatory, anti-catabolic, and pro-anabolic effects on cartilage and the synovial membrane. Mechanical loading of joint tissue directly affects the homeostasis of matrix degrading enzyme production and matrix repair.

Objectives: To explore the impact of diacerein and moderate mechanical stimulation on the anabolic metabolism of OA and non-OA chondrocytes, as well as on the integrin-FAK-MAPKs signal transduction cascade in these cells.

Methods: Mechanical stimulation was applied in terms of three different intensities by the Flexcell tension system. Influence on catabolic parameters such as MMPs, ADAMTS, and IL-6 were assessed by qPCR. Changes in phosphorylation of FAK, STAT3 as well as MAP kinases were verified by western blot analysis. Intracellular calcium was measured fluorimetrically using fura-2.

Results: Mechanical stimulation at moderate intensity (SM/SA) proved to be most efficient in terms of reducing production of matrix degrading enzyme and IL-6 expression. Treatment with diacerein by itself and diacerein in combination with SM/SA reduced phosphorylation of FAK and STAT3, which is more pronounced in OA cells. Pretreatment with diacerein for 7 days resulted in an increase in the sensitivity to Yoda1, the agonist for the mechanically activated ion channel Piezo1. However, in OA cells a significant reduction in Piezo1 expression was observed following treatment with diacerein.

Conclusions: Cyclic tensile strain can reduce matrix destroying enzymes, and when used in combination with diacerein, the activity of integrin signalling components is changed. The observed effects can be mainly attributed to diacerein's capacity to modulate STAT3 and Piezo1, which are both potential targets to prevent the progression of OA.

Disclosure of Interest: None declared

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AB0092 IL37 INHIBITS PROTEOGLYCAN LOSS IN HUMAN OA CARTILAGE: LINK BETWEEN IL37 AND MMP3

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Background: Glycosaminoglycans (GAGs) are essential for the pressure-resistant function of cartilage. During osteoarthritis (OA), GAGs are lost from cartilage. This loss impairs the functional and structural integrity of cartilage, thereby accelerating further cartilage damage. Proteoglycan degradation is mediated by enzymes such as MMP3, MMP13 and ADAMTS5.

Objectives: Recently we discovered that interleukin 37 (IL37) lowers the expression of these enzymes in human OA chondrocytes. The goal of this study was to investigate if IL37 protects against GAG loss in freshly obtained human OA explants.

Methods: Human cartilage was obtained from ten OA patients undergoing total knee or hip arthroplasty. Per condition 6 cartilage explants of 4 mm in diameter were used. Explants were incubated with recombinant IL37 (rhIL37) for up to 6 days. Every other day new rhIL37 was added. Additionally, an MMP3-inhibitor, or MMP13-inhibitor or ADAMTS5-inhibitor was added in the same protocol. Sulfated GAGs (sGAGs) were visualised by histology, and sGAG release in culture medium was quantified using 1,9-dimethylmethylene blue. To study sGAG synthesis, explants were incubated with rhIL37 followed by 4 hour labelling with ³⁵SO₄. Alternatively, explants were pre-labelled for 4 hour with ³⁵SO₄ followed by incubation with rhIL37 to study sGAG degradation. Additionally, expression levels of proteoglycans and cartilage matrix degrading enzymes were measured by qPCR and Western Blot. Activity of MMP and ADAMTS enzymes was determined by measuring FFGV, ARGS and NITEGE neo-epitope levels in the supernatant of the cultures, using ELISA.

Results: Culturing human OA explants for up to 6 days, caused a reduction in GAG content as observed by loss of Safranin O staining. In addition, a release of sGAGs was measured in the supernatant of on average 17,5 µg/ml per mg cartilage. Incubation of cartilage explants with rhIL37 significantly reduced the release of GAGs. A maximal reduction of 24% was already observed with the lowest dose of rhIL37 (1 ng/ml). No effect of rhIL37 on the amount of incorporated ³⁵SO₄ was observed, indicating that rhIL37 does not alter the synthesis of GAGs. This is supported by the observation that rhIL37 does not affect the mRNA expression of the large proteoglycans and SLRPS. In contrast, we did find that rhIL37 significantly reduced the loss of ³⁵SO₄-labelled GAGs from cartilage explants. In addition, rhIL37 reduced MMP3 and MMP13 protein expression and lowered both MMP and ADAMTS mediated degradation of proteoglycan fragments: FFGV neo-epitope and ARGS and NITEGE neo-epitopes, confirming that rhIL37 reduces active degradation of sGAGs. Lastly, to investigate which proteolytic enzyme contributes to the sGAG release in our culture system, a MMP3-, MMP13- or ADAMTS5-inhibitor was added to the explants. Strikingly, we found that only MMP3 inhibition mimicked IL37 function, suggesting that the effects of rhIL37 run via MMP3.

Conclusions: Our data show that rhIL37 reduces sGAG release of cartilage explants, indicating that IL37 supports cartilage matrix integrity. To our knowledge this is the first report demonstrating this anti-destructive effect of IL37 on freshly

obtained human OA cartilage explants. Possible these effects run via MMP3 because IL37 reduced MMP3 expression and only MMP3 inhibition results in similar effects as rhIL37 addition.

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AB0093 NATURAL POLYMER-BASED HYDROGELS FOR CARTILAGE REGENERATION

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Background: Cartilage is a tough, flexible tissue found throughout the body. It can become damaged because of a sudden injury, such as a sports injury, or gradual wear and tear (osteoarthritis). Injured articular cartilage has a poor regenerative capability, for this reason, tissue engineering may provide a fundamental therapeutic solution to repair cartilage injury.

Human articular cartilages are composed of dense extracellular matrix and chondrocytes. One of the major components in the extracellular matrix is hyaluronic acid. The combination of hyaluronic acid with other natural polymers to prepare hydrogel scaffolds may be potentially useful in many tissue engineering applications, including cartilage regeneration.

Objectives: We propose the synthesis of hydrogels based on hyaluronic acid and chitosan by a new strategy of synthesis using di-isocyanates to obtain an interpenetrated network of chitosan and hyaluronic acid.

Methods: Different kinds of hydrogels were synthesised using hyaluronic acid (Bioibérica, Spain), natural polymers (gelatine, chitosan) and stabilised with diisocyanates. The hydrogels were charged with chondroitin sulfate (Bioibérica, Spain).

Morphological Characterisation: The hydrogels were characterised by scanning electron microscopy and energy dispersive X-ray microscopy in order to study the morphology and the composition of the hydrogels.

Hydrogel Swelling: Dynamic swelling experiments were performed by placing discs of stabilised hydrogels in PBS at 37.0°C, and measuring their weight gain as a function of time.

Biocompatibility: Cytotoxicity *in vitro* assays (MTT) and cell adhesion tests (Alamar Blue) were performed on the hydrogels using different cell lines to corroborate the biocompatibility of the hydrogels.

Results: All the synthesised hydrogels presented a high interconnected porosity. The studied hydrogels swelled around 200%. After five hours equilibrium was reached and this equilibrium depended on the ratio hyaluronic acid/natural polymer increasing with the amount of hyaluronic acid present on the hydrogel. MTT assay indicated that the extracts collected at different times from the hydrogels were not cytotoxic and could be considered biocompatible. Cell adhesion assay demonstrated that the hydrogels supported cell adhesion and proliferation, and this behaviour was better on SC-loaded hydrogels.

Conclusions: Hydrogels based on hyaluronic acid and natural polymers are proposed as scaffolds for tissue engineering. The presence of interconnected porous and the good swelling properties, as well as the biocompatibility, represent a great advantage for application in cartilage regeneration. The addition of drugs or glycosaminoglycans is being studied to improve the cartilage regeneration.

Disclosure of Interest: None declared

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AB0094 POSITIVE EFFECTS OF CHIROPRACTIC MANIPULATION ON SUBCHONDRAL BONE MINERAL DENSITY, CARTILAGE DAMAGE AND SYNOVIAL INFLAMMATION IN OSTEOARTHRITIC RABBITS

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Background: Osteoarthritis (OA) is a degenerative joint disease characterised by the degradation and inflammation of cartilage and synovium with bone damage. Different approaches that decrease subchondral bone remodelling during OA have demonstrated to improve cartilage damage and synovial inflammation. Chiropractic is a therapeutic approach focused on the diagnosis, treatment and prevention of musculoskeletal disorders. Chiropractic manipulation (CM) is essentially manual, allowing the chiropractor to restore the normal range of motion and function of the joints, muscles, and ligaments. We have previously observed