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AB0291E

THE EFFECT OF HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS-DERIVED EXOSOMES ON CHEMOKINES IN COLLAGEN-INDUCED ARTHRITIS RATS

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Background: Umbilical cord mesenchymal stem cells (UCMSC) derived exosomes could simulate the function of MSC and avoid the limitations of MSC, which is being hotspot in the research of rheumatoid arthritis (RA) treatment. Chemokines can recruit inflammatory cells and osteoclasts in inflammatory joints, and participate in the synovial inflammation and bone destruction of RA. The mechanisms of UCMSC-derived exosomes on chemokines have less understood in RA

Objectives: The aim of this study was to investigate the effect of UCMSC and UCMSC-derived exosomes on the chemokines CCL2, CXCL10 and CXCL12 in CIA rats.

Methods: Human umbilical cord mesenchymal stem cells (UCMSCs) were cultured in vitro and separated using a differential centrifugation methods. The CIA rats model was set up by Freund's complete adjuvant and type II collagen, then randomly divided into control, CIA, MTX, UCMSCs, UCMSCs exosomes low and high concentration groups. Rats in UCMSCs group were injected in double ankle joint with UCMSCs 2X10⁶/L weekly for 3 weeks. Rats in UCMSCs exosomes low and high group were injected in double ankle joint with UCMSCs exosomes 30μg and 90μg weekly for 3 weeks, respectively. Rats in MTX group were given intraperitoneal injection with MTX (0.9mg/kg) weekly for 3 weeks. Serum concentrations of CCL2 and CXCL10 were detected by flow cytometry. CXCL12 serum level was tested by enzyme-linked immunosorbent assay (ELISA). The protein expressions of CCL2, CXCL10 and CXCL12 in synovial tissue were detected by immunohistochemistry. CCL2, CXCL10 and CXCL12 mRNA levels in synovial joint and spleen were measured by reverse transcription-polymerase chain reaction (RT-PCR).

Results: Intra-articular injection of UCMSC exosomes decreased CCL2 and CXCL12 levels in serum and improved synovial hyperplasia and inflammatory cell infiltration in the CIA rats. UCMSC exosomes suppressed the protein expressions of CCL2, CXCL10, CXCL12 in synovial tissue. It also inhibited transcript levels of CCL2, CXCL10, CXCL12 in synovial tissue and spleen. UCMSC had similar effect on CCL2, CXCL10, CXCL12 in CIA. The high concentration group was more effective than the low concentration in preventing CCL2, CXCL10, CXCL12 protein expressions of synovial tissue and CCL2 transcript level of spleen.

Conclusion: UCMSC exosomes alleviates synovial inflammation in CIA rats through suppression of CCL2, CXCL10, CXCL12 release. The inhibitory effect of on chemokines simulate UCMSC, their cell of origin, the high concentration was better than low concentration.

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Rheumatoid arthritis - comorbidity and clinical aspects

AB0292

EFFECTS OF ACETAMINOPHEN ON THE KIDNEY FUNCTIONS OF PATIENTS WITH MUSCULOSKELETAL DISEASE TREATED WITH LONG-TERM NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY

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Background: While nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently used therapeutic agents, they are known to cause side effects, such as gastrointestinal disorders and kidney dysfunction. As the proportion of patients with chronic kidney disease (CKD) increases with age, dealing with NSAIDs requires particular care in areas with aging populations. However, in many cases, prescriptions are continued without any particular plan. Hence, the effects of acetaminophen (AAP), which does not cause kidney dysfunction, are being revisited. Opportunities are increasing for using formulations containing tramadol hydrochloride in patients with chronic pain or intravenous agents for perioperative pain management.

Objectives: In this study, we investigated the kidney functions of patients with musculoskeletal disease who had been using NSAIDs for a long time and examined the possibility of switching to AAP.

Methods: The subjects were 105 patients with musculoskeletal disease (42 men and 63 women) who were being treated as outpatients in the orthopedics department of our hospital and had been using NSAIDs for at least 3 months. They primarily had 5 musculoskeletal diseases, including degenerative osteoarthritis (OA), rheumatoid arthritis (RA), osteoporosis (OP), polymyalgia rheumatica (PMR), and gout (G). After checking their background characteristics, we measured their kidney functions and visual analogue scale (VAS) scores, and then switched them from NSAIDs to AAP. Kidney functions were evaluated by classifying CKD using glomerular filtration rate (eGFR) and urinary protein, and by using the Cockcroft-Gault equation to calculate creatinine clearance (Ccr). The patients were given the NSAIDs that they had been taking for single use. Six months after the switch, we remeasured their kidney functions and VAS scores, and investigated whether they could continue using AAP and whether they had used NSAIDs.

Results: The patients' mean age at the time of switching from NSAIDs to AAP was 76 years, and their mean duration of NSAID use was 43 months. For the diseases, 63 patients had OA, 20 had RA, 14 had OP, 6 had PMR, and 2 had G. Before the switch, the mean VAS score was 41.6 mm and mean eGFR was 67.0 mL/min/1.73 m². On the basis of the eGFR, the CKD classification was G3 or higher in 38.1% of patients. The CKD classifications with the amounts of urinary protein added to the eGFR were as follows: green, 44.7%; yellow, 33.0%; orange, 14.6%; and red, 7.8%, with 55.4% classified as having CKD. By age, the proportions of patients with CKD based on eGFR and CKD classification were as follows, respectively: 0.0% and 12.5% for those in their 50s, 16.7% and 25.0% for those in their 60s, 29.3% and 48.8% for those in their 70s, and 59.5% and 69.0% for those in their 80s and older. The mean AAP dose was 455 mg.

Six months after the switch, 69 patients had continuously used AAP without regular NSAID use. Of these patients, 13 had used NSAIDs for rescue purposes. Thirty-six patients had stopped using AAP, the most common reason being ineffectiveness (15 patients), although 9 patients did so because they no longer needed any analgesic. Three patients stopped using the drug owing to palpitations or other side effects, although none stopped because of liver dysfunction. Overall, the mean VAS score declined significantly as compared with before the switch, as did the mean eGFR. Of those who continued to use AAP, 56 patients who did not use any NSAIDs exhibited significantly lower mean VAS scores, but not a significant decline in mean eGFR.

Conclusion: The proportion of patients with CKD who were receiving long-term NSAID therapy was higher than that of the general population for all age groups. Halting NSAIDs and switching to AAP could help maintain kidney functions, which could continue to decline with NSAID use.

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AB0293

ASSOCIATION OF HOMOCYSTEINE WITH BONE MINERAL DENSITY IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with unknown etiology that primarily affects the peripheral joints and, over time, leads to loss of mobility if untreated. RA is an important risk factor of osteoporosis and occurrence of fractures. Many authors describe a significantly higher frequency of osteoporosis and fractures in patients with RA in comparison to a control group. The aetiology of progressive bone mass loss in RA patients is multi-factorial and remains obscure. Factors related to the pathological process – activity of RA and applied therapy – seem to be significant. Homocysteine (Hcy) is a sulfhydryl containing amino acid produced by demethylation of an essential amino acid (methionine). A high serum level of Hcy has been recently recognized as a risk factor for osteoporosis and osteoporotic fractures in postmenopausal women.

Objectives: The purpose of this study was to evaluate serum Hcy levels in RA patients compared with healthy controls, examine possible associations between Hcy and bone mineral density.

Methods: This cross-sectional study was performed in Vega-Baja Hospital, Orihuela (Spain) from November 2016 to May 2018. We prospectively enrolled 63 consecutive women patients affected by RA and followed at the Vega-Baja Hospital (Orihuela, Spain) and 60 matched healthy women controls. All patients included in this study had normal serum creatinine (Cr) levels and met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA. Serum Hcy was analyzed using immunonephelometric method. Bone mineral density (BMD) of femoral neck and lumbar spine was measured by dual-energy X-ray absorptiometry (DXA).

Results: A total of 63 female patients were included in our study, with a mean (SD) age of 53 ± 8 years. The majority were Caucasian (90.5%). Thirty-four patients were menopausal and twenty-nine non-menopausal patients. The mean duration of RA was 8.5 ± 5.8 years. The mean disease activity scores in 28 joints (DAS28) according to the erythrocyte sedimentation rate (ESR) indicated low disease activity 3.0 ± 1.3 . The mean health assessment questionnaire (HAQ) was 0.75 ± 0.67 . Twenty-eight patients were treated with methotrexate, with a median weekly dose of 11.5 ± 4.8 mg, all the patients received 10 mg folic acid supplementation per week. Serum Hcy concentrations were significantly higher in the RA patients than those in the control group: 9.93 (5.6 – 18.8) vs. 7.11 (4.9 – 11.1), pg/mL ; $P < 0.001$. Serum levels of Hcy were inversely related to lumbar spine BMD and femur neck BMD ($r = -0.28$; $P < 0.05$).

Conclusion: Patients with RA have high levels of Hcy that correlate, inversely, with bone mass suggesting that hyperhomocysteinemia is a risk factor for osteoporosis in patients with RA.

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AB0294

THE EFFECT OF SMOKING ON ENDOTHELIN-1 IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis (RA) is one of the chronic autoimmune diseases with an estimated prevalence of 1 to 2 percent of the total population in the world. RA patients have an increased risk of morbidity and mortality from cardiovascular (CV) events as a result of accelerated atherosclerosis. Endothelin-1 (ET-1) is a hormone with strong vasoconstrictor properties, secreted in excessive amounts by damaged endothelial cells. However, the effect of this hormone depends on the presence of specific ET-1 receptors as well as their density and location. ET-1 is a mediator-activating autocrine and paracrine, primarily in the circulatory system. It induces the production of proinflammatory cytokines, exacerbating the inflammatory process.

Objectives: The objectives of this study were: to compare serum ET-1 levels between RA patients and healthy controls and observe the relationship between tobacco smoking and serum levels of ET-1 in RA patients.

Methods: This cross-sectional study was performed in Vega-Baja Hospital, Orihuela (Spain) from November 2016 to May 2018. We prospectively enrolled 63 consecutive women patients affected by RA and followed at the Vega-Baja Hospital (Orihuela, Spain) and 65 matched healthy women controls. All patients included in this study had normal serum creatinine (Cr) levels and met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA. Current smokers were defined as those who reported having smoked ≥ 1 cigarette per day regularly during the year preceding the examination. Serum ET-1 was analyzed using ELISA.

Results: A total of 63 female patients were included in our study, with a mean (SD) age of 53 ± 8 years. The majority were Caucasian (90.5%). The mean duration of RA was 8.5 ± 5.8 years. The mean disease activity scores in 28 joints (DAS28) according to the erythrocyte sedimentation rate (ESR) indicated low disease activity 3.0 ± 1.3 . The mean health assessment questionnaire (HAQ) was 0.75 ± 0.67 . Fourteen (22%) patients had a smoking history. Serum ET-1 concentrations were significantly higher in the RA patients than those in the control group: 30.6 (0 – 50) vs. 21.7 (0 – 50), pg/mL ; $P < 0.001$. Higher plasma ET-1 concentrations were significantly associated with smoking ($r = 0.29$; $p < 0.05$).

Conclusion: Our data shows a significant difference in the concentration of serum ET-1 between RA patients and controls. We report significant positive association between serum levels of ET-1 and smoking status.

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