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Original Research Article

Effects of Walking Exercise and Meloxicam on MMP-13 Expression and Pain Threshold in Osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a chronic joint disease driven by pro-inflammatory cytokines TNF-α and IL-1, which elevate matrix metalloproteinase (MMP) levels and impair extracellular matrix (ECM) synthesis. While NSAIDs are commonly used to manage OA, their long-term side effects highlight the need for alternative therapies. This study aims to examine the effects of walking exercise and meloxicam on MMP-13 expression and pain threshold. OA was induced in 30 Rattus norvegicus with a 2 mg Monoiodoacetate (MIA) injection in 25 µL saline. The animals were randomly assigned into five groups: (K-) received saline only, (K+) received MIA only, (T) received MIA and a 10 m/minute light-intensity treadmill exercise, (TM) received MIA, a 10 m/minute light-intensity treadmill exercise, and oral meloxicam (1mg/kg), and (M) received MIA and oral meloxicam (1mg/kg). The treatments were administered as treadmill exercises (30 minutes/day, 5 days/week) for 6 weeks, and meloxicam was given orally (1 mg/kg, 5 days/week) for 6 weeks. After the 6-week treatment period, immunohistochemical analysis was performed to evaluate MMP-13 expression in joint cartilage tissue, and pain threshold were measured pre- and post-treatment using an analgesiometer. The results revealed that group T experienced a significant reduction in MMP-13 expression (p-value = 0.00) and an increase in pain threshold values (p-value = 0.00). These findings suggest that walking exercise can effectively suppress MMP-13 expression and increase pain threshold in OA.

Keywords: Osteoarthritis, walking exercise, pain, matrix metalloproteinase, meloxicam

Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by the progressive loss of cartilage and subchondral bone.[1] About 80% of individuals with OA experience movement limitations, 25% encounter difficulties in performing daily activities, and approximately one-third suffer from some form of disability.[2] The etiology of OA is believed to stem from biomechanical and molecular changes in the joint, influenced by factors such as aging, obesity, injuries, joint misalignment, and inflammation.[2] A hallmark feature of OA is the degradation of articular cartilage (AC), which also affects the synovial membrane. Components of AC, primarily type II collagen and aggrecan, as well as subchondral bone and surrounding soft tissues, undergo destruction, resulting in joint dysfunction. Common clinical symptoms of OA include pain, knee swelling, stiffness, and reduced physical activity.[3] Biomarkers linked to cartilage degeneration include matrix metalloproteinase (MMP), a disintegrin, and metalloproteinase with thrombospondin type-1 motifs (ADAMTS) family. Among these, MMP-13 is the principal enzyme responsible for cartilage breakdown.[4] In OA, the extracellular matrix (ECM) of the synovial joint is degraded, leading to severe pain in affected patients.[4] molecule aggrecan, so it has a dual role in matrix damage.[5]

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Immune cells produce many inflammatory mediators, such as TNF-a, IL-1, and IL-7, which stimulate the production of MMPs capable of degrading all ECM components. MMP-13, in addition to degrading collagen, also targets the proteoglycan Current management of OA-related pain and inflammation primarily involves non-steroidal anti-inflammatory drugs (NSAIDs), with meloxicam being one of the most commonly prescribed options.[2] As a selective COX-2 inhibitor, meloxicam has demonstrated effectiveness and tolerability comparable to diclofenac, a targeted anti-inflammatory medication for osteoarthritis. However, prolonged use of NSAIDs can result in significant side effects, such as gastric ulcers and kidney impairment, particularly in older populations.[4] This underscores the necessity for alternative therapies to reduce dependence on long-term pharmacological treatments.

Physical exercise has been shown to play a critical role in preventing and managing several chronic conditions, including OA. The mechanical stress induced by the exercise can modulate the signaling pathways of inflammatory mediators involved in OA pathophysiology (IL-1β, TNF-α, IL-6, and INF-γ), supporting proteoglycan and collagen synthesis while slowing the progression of joint damage, according to Sakamoto (2023)[5]. Furthermore, physical activity can elicit an anabolic and protective response by increasing the expression of anti-inflammatory cytokines (IL-10 and IL-4), which help mitigate the production of reactive oxygen species (ROS).[6]

Based on the above explanations, this study aims to investigate the effects of regular walking and meloxicam administration on MMP-13 expression and pain threshold in rat models of osteoarthritis.

Materials and Methods

Study Design

This study involved 30 Rattus norvegicus rats, each weighing between 200 and 250 grams. The animals were housed in cages measuring 30 × 40 × 20 cm, with five rats per cage, under a controlled 12-hour light-dark cycle at an ambient temperature of 25°C. Food and water were provided ad libitum. The rats were divided into five groups: (K-): saline injection only; (K+): Monosodium iodoacetate (MIA) injection only; (T): MIA injection followed by light-intensity treadmill exercise at 10 m/minute; (TM): MIA injection followed by treadmill exercise at 10 m/minute and oral meloxicam administration (1 mg/kg); and (M): MIA injection with oral meloxicam administration (1 mg/kg). The primary parameters assessed were MMP-13 expression in joint tissue and pain threshold values.

Osteoarthritis Models

Osteoarthritis (OA) was induced using monosodium iodoacetate (MIA) (cat#12512; Sigma, St. Louis, MO, USA) dissolved in 25µL of saline solution at a dose of 2 mg.[6] Following the injection, the rats were rested for one week. OA confirmation was performed using radiographic (X-ray) examination.[10]

Radiographic examination

The radiographic examination was performed after the OA induction. The procedure used an Agfa 24/30 cassette divided into six equal zones, placed on a Shimadzu conventional device table. The rats' knee was disinfected, taped, and positioned for a vertical X-ray beam directed toward the cassette. Constant parameters for voltage (Kv), weight, and duration (seconds) were maintained. The knee images were classified based on the Kellgren and Lawrence grading system, which evaluates osteophytes and joint space narrowing into four categories: doubtful, minimal, moderate, and advanced, providing a comprehensive assessment of the osteoarthritic condition in the examined subjects.[5]

Walking exercise treatment using a treadmill. The walking exercise treatment was conducted in the Bioscience Laboratory, Universitas Brawijaya. The rats were acclimatized to the treadmill environment for three days. Previous studies indicated maximum oxygen uptake at different treadmill speeds (29.8% at 10 m/minute, 46.7% at 15 m/minute, and 63.8% at 20 m/minute).[13] The intensity of endurance in humans ranges from 20% to 39% of maximum oxygen. Based on these findings, light-intensity treadmill exercise was set at 10m/minute, mimicking normal human walking, for 30 minutes/day, 5 days/week, over six weeks.[9]

Anti-inflammatory treatment with meloxicam

One week after MIA injection, rats in the TM and M groups received meloxicam at a dose of 1 mg/kg body weight. As meloxicam is insoluble in water, it was dissolved in a mixture of polyethylene glycol 400 (PEG 400) and water (50:50). The drug was administered daily via oral gavage for five days per week over six weeks, preceding the treadmill exercise.[19]

Measurement of pain threshold values with analgesiometer

The pain threshold measurement targeted the right knee joint. Pre-treatment evaluations were performed one week post-MIA injection, and the final evaluations were conducted during the last week of the treadmill exercise. The pain was measured using an analgesiometer (Ugo Basile, Varese, Italy) by applying gradual mechanical pressure (48 g/s) to the lateral side of the right knee. The rats were placed in a sleeve with their hind legs exposed during the procedure.[7,10]

Histopathological tissue sampling and preparation

After six weeks of treatment, the rats were anesthetized using ketamine (35 mg/kg), and their right knee joints were dissected. Cartilage samples from the femur and tibia were collected using surgical instruments. [13] The histopathological preparation of the joint tissue followed the established protocols, which were fixation in 10% formaldehyde for 24 hours, decalcification with EDTA, and dehydration through graded alcohol solutions. Subsequently, the tissues were clarified in xylene, impregnated in liquid paraffin, embedded in paraffin blocks, and then sectioned at 4-5 µm thickness using a microtome. [6,8]

Joint Tissue Examination Procedure by Immunohistochemical Method

The immunohistochemical staining followed a standard protocol. The tissues were treated with 85% and 100% propylene glycol solution, 0.5% and 10% formalin, MMP-13 antibody, and distilled water 1: 400 (Diluent 399µL and 1µL antibody). The samples were then immersed in xylol for 5 minutes (repeated three times), mounted with Entellan, and covered with cover glass. The prepared slides were air-dried before examination.[8,11]

Data Analysis

The data were analyzed using SPSS software. Differences in MMP-13 expression among treatment, positive control, and negative control groups were evaluated using one-way ANOVA. The pain threshold values were analyzed using two-way ANOVA followed by Tukey HSD post hoc tests.

Results and Discussion

In this study, osteoarthritis (OA) was induced using Monoiodoacetate (MIA), resulting in significant pathological changes, including cartilage surface erosion, matrix degradation, and cellular death. Figure 1 illustrates the time-dependent progression of MIA-induced joint pathology through radiographs of the tibiofemoral knee joint captured at weekly intervals. Furthermore, Figure 2(A) presents the immunohistochemical staining of MMP-13 expression in knee joint cartilage, where brown staining indicates the percentage of positively stained cells. The statistical analysis, depicted in Figure 2(B), demonstrates a significant reduction in MMP-13 expression in the treatment group compared to the MIA control group (p-value 0.00 <0.05).

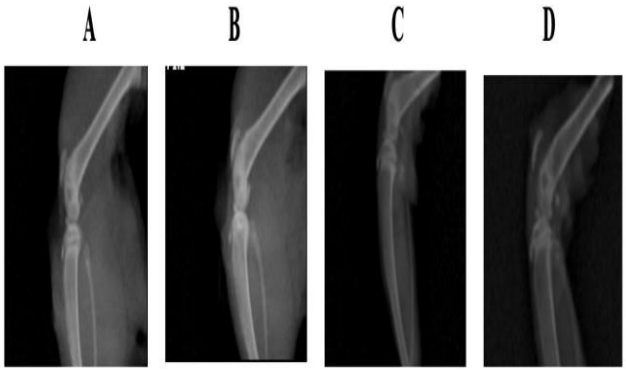

Figure 1. Radiographic representation of an animal model of osteoarthritis (OA) induced by Monoiodoacetate (MIA). Joint pathology was observed from weeks 1 to 3. Panel A shows the healthy control group, where no osteophytes, joint gap narrowing, or sclerosis are present, as assessed using the Kallgren & Lawrence scale. Panel B illustrates the MIA injection group in the first week, showing grade 2 OA. Panels C and D depict weeks 2 and 3, where grade 3 OA is evident, characterized by osteophytes, joint gap narrowing, and sclerosis.

The initial pain threshold measurements were conducted one week after the MIA or saline injection. Figure 3 reveals a statistically significant difference in pain threshold values between groups (p-value = 0.00) both pre- and post-treatment. During the first week, MIA-injected groups exhibited lower analgesiometer test results than the saline-injected group. After treatment, only the control group that received MIA maintained a low pain threshold, while the treatment groups exhibited significant improvements in pain threshold values when compared to the pre-treatment levels.

These findings are in line with previous research by Pajak et al. (2017)[17], who reported that meloxicam administration in OA rat models decreased MMP-13 expression in cartilage tissue. This reduction is believed to result from the inhibition of inflammatory pathways that stimulate MMP-13 expression, such as prostaglandins and pro-inflammatory cytokines.[17] Similarly, Hu[18] observed that meloxicam administration reduced MMP-13 expression in OA rat models, which et al. (2002)[20] found that meloxicam reduced pain sensitivity in OA animal models by inhibiting inflammatory processes and decreasing the release of pain mediators such as prostaglandin E2.[20]

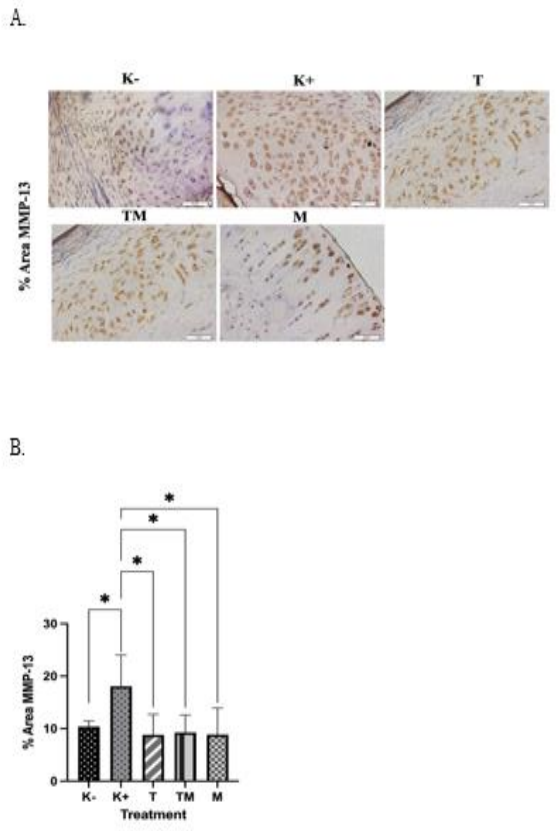

Figure 2. (A) Immunohistochemistry on knee joint tissue, showing the intensity of MMP-13 immunohistochemical staining in the cartilage tissue of each group and the percentage of positively stained cells indicated by the brown color. (B) Statistical analysis of MMP-13 expression in knee joint tissues: (K-) saline injection only, (K+) MIA injection only, (T) MIA injection and 10 m/minute light-intensity treadmill exercise, (TM) MIA injection, 10 m/minute light intensity treadmill exercise, and oral meloxicam (1 mg/kg), (M) MIA injection and oral meloxicam (1mg/kg). The asterisk (*) denotes a significant difference ($p < 0.05$).

Physical activity is a widely recognized non-pharmacological intervention for managing OA. This study demonstrates that engaging in regular walking exercises significantly reduces MMP-13 expression, aligning with prior research suggesting that treadmill exercise alleviates cartilage lesion severity. Yang et al. (2017)[13] reported that treadmill exercise significantly attenuated the expression of IL-1β, TNF-α, MMP-13, and NF-κB p65. Molecular studies suggest that specific biomechanical stimuli and cellular interactions can generate intracellular signals, which either amplify or suppress pro-inflammatory cytokine activity in chondrocytes. Similarly, Silva (2017)[21] found that treadmill exercise effectively inhibited pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β, and IL-6) while enhancing anti-inflammatory was associated with decreased cartilage damage and inflammation. The decrease in MMP-13 is also thought to be related to the inhibition of cyclooxygenase-2 COX-2, which is the main target of meloxicam.[18]

Hu et al. (2021)[19] assessed the effect of meloxicam on pain threshold values using a pressure suppression test in OA rat models, reporting that its administration significantly increased the pain threshold, indicating its analgesic benefits in managing OA-associated pain.[19] Similarly, Del cytokines (IL-4, IL-10, and TGF-β).[21] Furthermore, Oka[7] reported that treadmill exercise reduces MMP-13 expression, primarily by mitigating mechanical stress.[7]

Catabolic changes in osteoarthritis OA-affected joints result in the elevated expression of collagenases and aggrecanases, which drive the degeneration of cartilage extracellular matrix (ECM) – a hallmark of OA pathogenesis. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 play a critical role in exacerbating these changes by increasing the production of matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), cathepsins, and inflammatory mediators including COX-2, iNOS, and PGE2 in both chondrocytes and synoviocytes.[12,14] Chondrocyte-derived MMPs are the primary enzymes responsible for degrading cartilage collagen and proteoglycans. Particularly noteworthy is MMP-13, which, when activated through the catabolic cascade instigated by pro-inflammatory cytokines, plays a pivotal role in the breakdown of type II collagen, significantly impacting the pathogenesis of OA. [12,13]

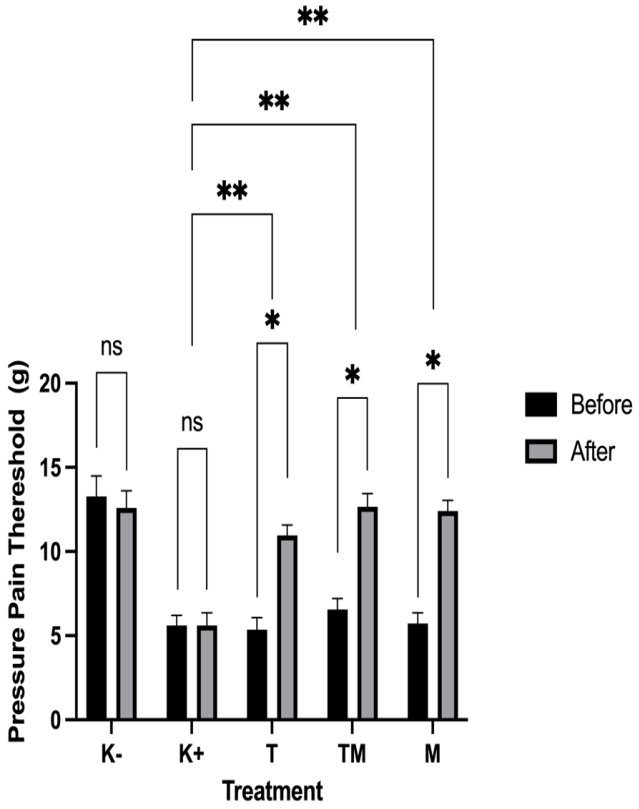

Figure 3. Pain threshold value pre- and post-treatment: (K-) saline injection only, (K+) MIA injection only, (T) MIA injection and 10m/minute light-intensity treadmill exercise, (TM) MIA injection, 10 m/minute light-intensity treadmill exercise, and oral meloxicam (1 mg/kg), (M) MIA injection and oral meloxicam (1 mg/kg). The asterisk (*) and double asterisks (**) denote significant differences ($p < 0.05$).

Anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 play essential roles in regulating inflammatory processes, although their effectiveness varies depending on the target cells.[14] Interleukin-4 (IL-4), when studied *in vitro* on OA tissues, has demonstrated the ability to

suppress the synthesis of TNF-α and IL-1β, similar to the effects of low-dose dexamethasone. Anti-inflammatory cytokines like IL-10, which naturally occur in the body, inhibit the synthesis of IL-1 and TNF-α, making them potential therapeutic targets for osteoarthritis management.[13]

Chondrocytes, synoviocytes, and macrophages are the primary producers of cytokines, with chondrocyte-generated mediators not entering systemic circulation but instead circulating through interstitial and synovial fluid.[15] Cytokines contribute to pain in two ways: first, by promoting the production of classic pain mediators, such as prostaglandins, that activate nociceptive neurons; second, by directly interacting with nociceptive sensory neurons, which express receptors for cytokines such as TNF-α and IL-1β.[15] Orita et al. (2011) [16] found a positive correlation between TNF-α levels in synovial fluid and pain intensity in the knee of OA patients, although no significant correlation was found with radiographic grades, and TNF-α levels were lower in the latter stages of the disease. [16]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used agents for managing OA pain. However, they are recommended for periodic or short-term use due to their potential side effects. Meloxicam, an NSAID, works by inhibiting cyclooxygenase (COX) enzymes, especially COX-2, which plays a significant role in the inflammatory process.[20] This decrease in inflammation helps decrease the release of pro-inflammatory cytokines and other mediators that can stimulate MMP-13 production. Several studies have shown that meloxicam administration in OA animal models can reduce MMP-13 expression, slowing cartilage damage and improving joint health. This suggests that meloxicam has the potential to modulate MMP-13 expression by attenuating inflammation.[18]

Conclusion

The results of this study indicated that regular walking at light intensity (10m/minute) for six weeks can reduce MMP-13 expression and increase the pain threshold in Osteoarthritis (OA). These findings are expected to provide valuable insights for formulating effective management strategies for OA patients.

Conflict of Interest

The authors declare no conflict of interest.

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Authors' Contributions

The study was conceived by DAP, KH, NK CSW, who also designed, drafted, reviewed, and edited the manuscript. The writing was carried out by KH, DAP, NK, and CSW, who also analyzed the literature. All authors have read and approved the final version of the manuscript. Data authentication applies to the study.

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