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The therapeutic benefits of NSAIDs and physical therapy in knee osteoarthritis

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Abstract

Introduction: Osteoarthritis (OA) has been established as a progressive wear and tear disease of the synovial joints, which also involves a certain degree of inflammation. Considering there is no disease modifying medication available at the moment, the current guidelines focus on the symptomatic treatment of the affection. Our study aimed to evaluate the therapeutic advantages of the synergistic use of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy in the treatment of knee osteoarthritis (KOA). *Patients, Materials and Methods*: The study comprised 46 individuals who were diagnosed with KOA and were admitted to the Department of Physical Medicine and Rehabilitation at the Emergency Clinical County Hospital of Craiova, Romania, between January 2021 and April 2022. All the participants received the same combination of pharmacological (Diclofenac 150 mg/day, no more than 10 days/month as needed) and non-pharmacological treatment (a 24-week plan of physical therapy). *Results*: The patient group exhibited a statistically significant reduction in both the average Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (p=0.0142) and the average Visual Analog Scale (VAS) (p=0.0023). Additionally, there was a statistically significant increase in both the average Knee Outcome Survey–Activities of Daily Living (KOS–ADL) (p=0.0128) and the average Oxford Knee Score (OKS) (p=0.0023). The study found a significant positive correlation between higher VAS ratings and cholesterol levels (p=0.0092), but no significant correlation between VAS scores and triglyceride levels (p=0.0986). Patients were evaluated for a further 24 weeks beyond the conclusion of the research to see if surgical intervention was necessary during this time. *Conclusions*: Our investigation tracked the WOMAC, VAS, KOS–ADL, and OKS measurements in a cohort of patients with KOA. The results demonstrate that the utilization of NSAIDs in conjunction with physical therapy effectively alleviates pain and enhances joint functionality.

Keywords: knee osteoarthritis, NSAIDs, physical therapy.

Introduction

Osteoarthritis (OA) or osteoarthrosis is a condition that affects the synovial joints. It is characterized by the gradual breakdown and loss of the protective cartilage in the joint. This leads to both functional and structural changes throughout the entire joint, including the synovium, meniscus, ligaments, and subchondral bone [1, 2]. OA is more frequently found in patients than rheumatoid arthritis (RA) or any other type of disease that affects the joints [3].

OA has emerged as a prominent contributor to disability, particularly due to the growing elderly population and the escalating rates of obesity. Consequently, its prevalence has surpassed historical levels. In the last years, there has been more understanding into what causes pain in OA and its pathogenesis [4].

One of the most important causes of work loss in the United States is represented by OA, which costs their economy above 100 billion US dollars per year and affects at least 20 million people [5, 6]. The disease is also responsible for one of the top five healthcare associated costs in Europe [3].

Unquestionable factors have been found to be associated with a higher risk of developing OA. Some of these can be modified while others cannot. Such factors are represented by age, gender, higher body mass index (BMI; being overweight or obese), osteoarticular trauma or sport-related injuries, which could lead to instability of the joints or muscle laxity, repetitive stress on the joints, genetic predispositions, bone misalignments or other deformities, metabolic or endocrine disorders and having previously suffered from other types of rheumatic diseases [7]. As most types of arthritis are more frequent in women, and more than half of all the people suffering from arthritis are women, such is also the case with OA, the female sex representing a notable risk factor [8].

Each imaging method utilized in the screening, diagnosis and monitoring the evolution of arthritis has its advantages

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and limitations. Plain classical radiography is one of the simplest, cheapest and most frequently utilized imagistic methods used for OA. Simple radiography is used to visualize changes in the bone cortex, such as osteophytes, narrowing of the joint space, subchondral sclerosis, and the existence of subchondral cysts [9].

Another cost-effective imagistic exploration that can be complementary to radiography is represented by musculoskeletal ultrasound (MSUS). In comparison with classical radiological assessment, this method can give a better assessment of meniscal extrusions, tibiofemoral osteophytes and changes in the medial femoral cartilage as well as the evaluation of bursitis [10, 11].

Magnetic resonance imaging (MRI) has become he highest standard for OA evaluation due to its ability to assess the whole joint as an organ, to view modifications in multiple tissues at the same time and to also evaluate pre-morphological changes of biochemical compositional nature of the articular and periarticular tissues [10, 11]. Articular cartilage, menisci, ligaments, synovium, capsular structures, fluid collections and bone marrow represent several structures that cannot be visualized on simple radiography but which the MRI can assess [10]. Considering the high costs, this method is not routinely used, but it is usually a must before surgical procedures.

Regarding the treatment of OA, even though no disease-modifying medication exists at the moment [12], there are several methods of treatment ranging from non-pharmacological treatment (weight management, exercise, biomechanical interventions and the use of walking canes) to pharmacological therapy (oral, topical and intraarticular) and even surgery as a last case scenario when the first lines of management have failed [13, 14]. Various guides reviewing the recommendations of treatment by *Osteoarthritis Research Society International* (OARSI), *American Academy of Orthopaedic Surgeons* (AAOS), *American College of Rheumatology* (ACR) and others are available [14, 15].

Aim

The aim of our study was to evaluate the therapeutic advantages of using a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy techniques in reducing pain while improving knee function in individuals diagnosed with knee osteoarthritis (KOA).

Patients, Materials and Methods

Patients

The current study involved patients who were diagnosed with KOA based on the criteria established by the *ACR*. These patients were admitted to the Department of Physical Medicine and Rehabilitation at the Emergency Clinical County Hospital of Craiova, Romania, between January 2021 and April 2022.

The eligibility requirements consisted of being at least 18 years old, having a documented diagnosis of KOA, a Kellgren–Lawrence (KL) score of 2 or above, and experiencing pain for a period exceeding three months. The exclusion criteria included the presence of other joint diseases, autoimmune rheumatic illnesses, recent trauma, surgery, or infection that could have impacted joint physiology. Additionally, chronic organ failure and a recent history of neoplastic disease within the past five years were also considered as exclusion reasons.

The selected patients were subjected to physical examination, blood tests, antero-posterior and lateral incidence radiographs of the knees and depending on the evolution of the disease, patients on whom surgical intervention was necessary underwent an MRI scan of the respective knee. During the procedures, tissue samples were collected for histopathological (HP) assessment.

The evaluation encompassed an assessment of the patient's personal and family medical history, a comprehensive clinical examination, an evaluation of the nutritional status using the BMI, and an assessment of the knee joint through various methods including inspection, palpation, testing for joint effusion, and evaluating the range of motion (ROM) through both passive and active movements. Additionally, the ligaments and menisci were also evaluated.

In order to evaluate the knee's performance in everyday activities, we utilized the following measures: the Knee Outcome Survey–Activities of Daily Living (KOS–ADL), the Oxford Knee Score (OKS), and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index. The KOS–ADL contained a total of 14 questions, the first six regarding the symptoms while the last eight regarding function, scored from 5 to 0. With a score ranging from 0 to 70, a higher score signifies a better outcome while a lower score depicts a worse outcome. The OKS contained 12 questions, each scored from 4 – no problem to 0 – significant disability. The results from each question are summed into a score ranging from 0 to 48 with a higher score reflecting a better outcome and a lower score reflecting a worse outcome. The WOMAC had a total of 24 questions each scored from 0 to 4 as such: 0 – none, 1 – mild, 2 – moderate, 3 – severe, 4 – extreme. The questions were organized in three sections: "pain in the last 48 hours", "stiffness during the last 48 hours" and "difficulty in doing certain daily physical activities during the last 48 hours", each consisting of five, two and respectively 17 questions [16]. We also used the Visual Analog Scale (VAS) of 100 mm to assess the patients' pain.

The biological parameters that we measured are presented in Table 1.

Both anteroposterior and lateral radiographs were utilized to evaluate joint space, osteophyte formation, and subchondral sclerosis. We employed the KL scale for the purpose of grading [17].

The MRI knee protocol included the following sequences: sagittal proton density–fat saturation (PD–FS), coronal PD–FS, axial PD–FS, sagittal T1-weighted, coronal T1-weighted, sagittal T2-weighted, and sagittal oblique PD–FS for anterior cruciate ligament (ACL) evaluation.

The tissue fragments collected from the patients who underwent surgical procedures such as total knee replacement (TKR) or arthroscopy were processed by the usual HP technique and in accordance with the literature recommendations [18]. Sections of 0.3 cm were cut perpendicular to the surface of the cartilage, fixed in 10% neutral buffered formalin for 24–48 hours, subjected to decalcification for 4–6 weeks, then processed with the automatic tissue processor (Leica TP20), and later sectioned at 3–5 μm using the semi-automatic microtome (Leica RM2255). Each section was standard stained with

Hematoxylin–Eosin (HE; Leica CV5030 system) and Safranin O (CI50240, Sigma-Aldrich). The Safranin O staining method, in which the cartilage was stained in orange and the nuclei in black, was used for the detection of cartilage (evaluation of glycosaminoglycans).

Table 1 – ***Demographic, clinical, and laboratory data of the study group at baseline***

Sex (*n*, %)	40 females (86.96%)
	6 males (13.04%)
Age (mean, SD) [years]	67.61 (8.03)
Residence (*n*, %)	14 urban (30.43%)
	32 rural (69.57%)
Pain at mobilization (*n*, %)	42 (91.3%)
Crackles (*n*, %)	34 (73.91%)
ESR (mean, SD) [mm/h]	22.35 (10.15)
Cholesterol (mean, SD) [mg/dL]	196.91 (43.5)
Triglycerides (mean, SD) [mg/dL]	122.87 (57.53)
Total lipids (mean, SD) [mg/dL]	655.92 (138.83)
ALT (mean, SD) [U/L]	21.13 (8.47)
AST (mean, SD) [U/L]	20.04 (8.13)
FBS (mean, SD) [mg/dL]	108.74 (25.18)
sCr (mean, SD) [mg/dL]	0.78 (0.19)
BUN (mean, SD) [mg/dL]	44.87 (12.47)
WOMAC total index (mean, SD)	49.22 (4.99)
BMI (mean, SD) [kg/m^2]	34.91 (5.51)
KOS–ADL score (mean, SD)	34.30 (3.43)
OKS (mean, SD)	23.35 (2.44)
VAS (mean, SD) [mm]	55.57 (8.65)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar (glucose); KOS–ADL: Knee Outcome Survey–Activities of Daily Living; *n*: No. of cases; OKS: Oxford Knee Score; sCR: Serum creatinine; SD: Standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities.

We quantified the HP abnormalities identified on Safranin O or HE and Safranin O staining. On Safranin O-stained sections, we evaluated the loss of glycosaminoglycans by assessing the intensity of staining [19]. The HP evaluation involved examining Safranin O and HE-stained sections using the modified Mankin score, which assesses structure, cellularity, matrix staining, and tidemark integrity [20]. Additionally, the *OARSI* system was used to grade the cartilage morphology, ranging from grade 0 (intact) to grade 6 (deformation), with intermediate grades indicating various levels of damage such as surface discontinuity, fissures, erosion, and denudation [21].

Treatment and outcome

The patients were prescribed Diclofenac 150 mg/day, no more than 10 days/month as needed, therapeutic ultrasound (US), transcutaneous electrical nerve stimulation (TENS) and low-level laser therapy (LLLT).

The US was applied to both the knee joints using a topical anti-inflammatory gel as a medium (ultra-sonophoresis) in a 0.3 W/cm^2 dose, pulsed emission with a 1:1 ratio using a 5 cm transducer in a dynamic application pattern for 5 minutes. US was administered daily for a duration of 10 days at weeks 0 and 12.

Biphasic TENS was applied to the knee joint bilaterally using a dual-channel device with four electrodes measuring 5/5 cm each, in a cross-section pattern around the painful area. The frequency was set at 150 Hz and the intensity set at such a level only to cause a tingling sensation of the skin without causing muscle contraction or excessive discomfort. The duration of this procedure was established at 30 minutes, to be applied daily for 10 days at weeks 0 and 12.

The LLLT had 5 points of application on both knee joints, in a dose of 6 J/cm^2, with continuous frequency. The treatment was administered daily for a duration of 10 days, occurring at weeks 0 and 12.

The observation period was 24 weeks. The patients were examined at base and re-examined at 12 weeks and 24 weeks. WOMAC, KOS–ADL, OKS, and VAS were assessed at base and both re-examinations.

Statistical analysis

The statistical study was conducted using GraphPad Prism 9 for Windows. The unpaired *t*-test and the Pearson's/Spearman's coefficient were used to analyze the connection between the variables. Statistical significance was attributed to values of $p<0.05$. The summary statistics for continuous variables are reported as the mean ± standard deviation (SD).

Results

We investigated a total of 113 patients with KOA suspicion, of which we enrolled 51 patients for treatment. 46 of the patients completed both re-examinations. Of the five patients that did not finish the study, one was due to gastrointestinal (GI) side-effects (nausea) (Figure 1).

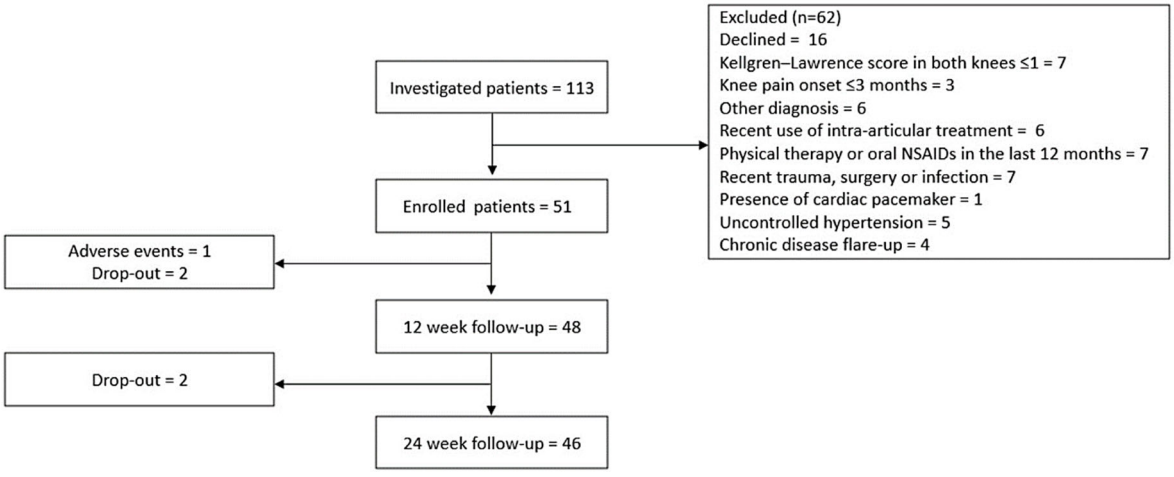

Figure 1 – ***Patient recruitment and follow-up diagram. NSAIDs: Non-steroidal anti-inflammatory drugs.***

The most frequent comorbidities encountered were arterial hypertension (86.96%), thyroid disorders (56.53%), type 2 diabetes (21.74%), chronic venous insufficiency (21.74%), and osteoporosis/osteopenia (21.74%).

13.05% of the patients had knee replacement surgery in one knee, while 30% of the women had undergone hysterectomy at some point in their lives.

In relation to the BMI, 4.35% of the patients had a normal weight, 8.70% were overweight, 43.47% had grade I obesity, 26.09% had grade II obesity, and 17.39% had grade III obesity.

More than half (56.52%) of the patients were on some form of dyslipidemia pharmacological treatment.

The radiological assessment (Figures 2–4) showed that 26.09% of the patients were categorized as grade 2, 43.48% were categorized as grade 3, and 30.43% were categorized as grade 4 using the KL scale, which is also displayed in Table 2.

Figure 2 – ***Radiograph of the knees in anterior view showing reduction of the joint space, predominantly in the medial compartment, subchondral sclerosis of the tibial plateau, and medial and lateral femoral and tibial osteophytes. R: Right.***

Figure 3 – ***Radiograph of the left knee in lateral view showing narrowing of the tibiofemoral and patello-femoral joint spaces, subchondral sclerosis of the tibial plateau, as well as patellar osteophytes. L: Left.***

Figure 4 – ***Radiograph of the knees in anterior view showing a reduction of the joint space, predominantly in the medial compartment, subchondral sclerosis of the tibial plateau, thinning of the tibial spines and femoral and tibial osteophytes. L: Left.***

Table 2 – ***Radiological classification using the KL grading system***

KL grade	*n* (%)
2	12 (26.09%)
3	20 (43.48%)
4	14 (30.43%)

KL: Kellgren–Lawrence; *n*: No. of cases.

From a clinical perspective, a higher grade on the KL scale was positively correlated with more significant symptoms and findings during the physical examination. More than one third of the patients classified as grade 3 had decreased both active and passive ROM in the knee joint, while more than half of the patients classified as grade 4 had knee pain present at all times, even at rest and at night, affecting the quality of sleep, with little response to medication. Most of the grade 4 patients presented difficulty in aspects of day to day life, such as walking and climbing the stairs.

WOMAC, KOS–ADL, OKS and VAS were recorded at baseline, week 12 and week 24. Mean values ± SD are presented in Table 3.

Table 3 – ***Baseline, week 12 and week 24 WOMAC, KOS–ADL, OKS and VAS scores***

	Baseline	Week 12	Week 24
WOMAC (mean, SD)	49.22 (4.99)	47.48 (5.45) *p*=0.2652	45.04 (6.04) *p*=0.0142
KOS–ADL (mean, SD)	34.30 (3.43)	35.26 (3.43) *p*=0.3493	36.52 (3.74) *p*=0.0419
OKS (mean, SD)	23.35 (2.44)	24.22 (2.65) *p*=0.2530	25.43 (2.98) *p*=0.0128
VAS (mean, SD)	55.57 (8.65)	51.30 (9.04) *p*=0.1096	46.65 (9.98) *p*=0.0023

KOS–ADL: Knee Outcome Survey–Activities of Daily Living; OKS: Oxford Knee Score; SD: Standard deviation; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities.

We observed a decrease of 3.54% (p=0.2652) in the average WOMAC score at week 12 and a decrease of 8.49% (p=0.0142) at week 24 compared to the initial measurement. The mean VAS also showed a decrease of 7.69% (p=0.1096) at week 12, and of 16.05% (p=0.0023) at week 24.

The average KOS–ADL score showed a 2.80% rise (p=0.3493) at week 12 and a 6.47% increase (p=0.0128) at week 24 compared to the initial measurement. Similarly, the average OKS increased by 3.73% (p=0.2530) at week 12 and by 8.91% (p=0.0023) at week 24.

There was no significant correlation between higher BMI and higher WOMAC (p=0.1817) score or higher VAS (p=0.3888). There was no significant correlation between cholesterol and triglyceride levels and WOMAC (p=0.1268; p=0.1768). Increased VAS scores were correlated with cholesterol levels (p=0.0092), but not with triglyceride levels (p=0.0986).

The ESR readings showed no significant correlation with either the WOMAC (p=0.7975) or the VAS (p=0.9159) ratings.

From the end of the second follow-up at week 24, we continued to monitor the patients for another 24 weeks. In this window, a total of 10 patients required either surgical intervention in the form of either TKR or therapeutic arthroscopy. MRI sample images from before the interventions are presented in Figure 5 (A and B) and

Figure 6 (A and B). Cartilage tissue fragments were collected during the surgical procedures for HP assessment.

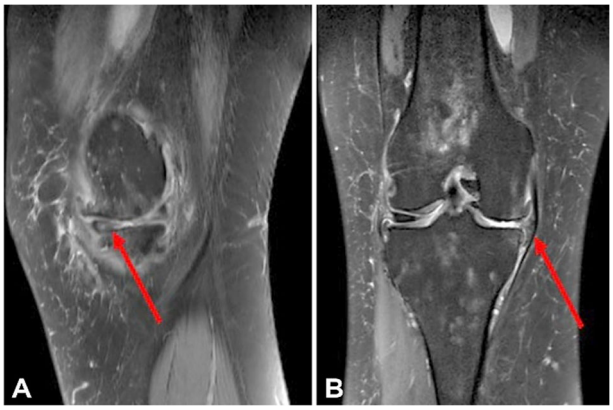

Figure 5 – ***3T MRI of the knee: (A) Sagittal PD–FS; (B) Coronal PD–FS. Both images reveal degenerative meniscal changes and a horizontal tear affecting both anterior and posterior horn of the medial meniscus, with medial meniscal extrusion and marginal femoral and tibial osteophytes that generate medial collateral ligament impingement. Also, image (B) reveals subchondral bone marrow edema affecting both the medial femoral condyle and the medial tibial plateau, with lack of visualization of both medial femoral and tibial cartilage, suggesting a grade IV chondromalacia. MRI: Magnetic resonance imaging; PD–FS: Proton density–fat saturation.***

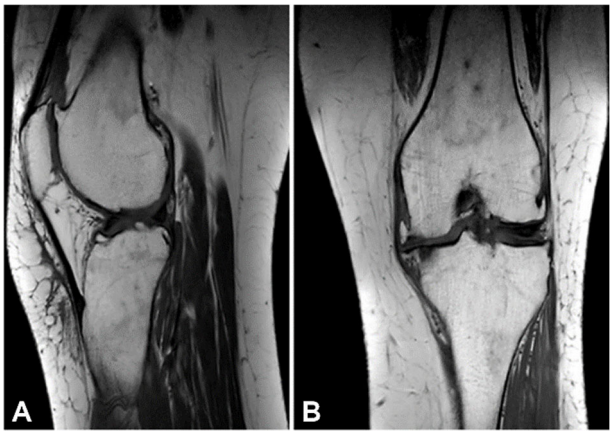

Figure 6 – ***3T MRI of the knee: (A) Sagittal T1; (B) Coronal T1. Both images reveal advanced knee degenerative changes, with marked marginal patellar, femoral and tibial osteophytes. Also, the tibiofemoral joint is greatly reduced in the medial compartment.***

The harvested cartilage fragments were placed in a 10% neutral buffered formalin solution and sent to the Pathological Anatomy Laboratory. Here they were embedded in paraffin, sectioned with a microtome and stained with HE. The microscopic examination highlighted the presence of parcelar necrosis, with fragmentation of the articular cartilage, microcracks, inhomogeneous arrangement of chondrocytes, alteration of the connective matrix and reduction in the number of chondrocytes (Figures 7–10).

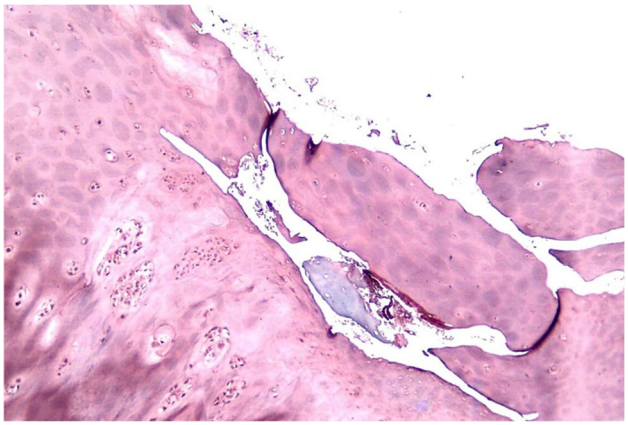

Figure 7 – ***Fragmented articular cartilage, with areas of necrosis. Hematoxylin–Eosin (HE) staining, ×100.***

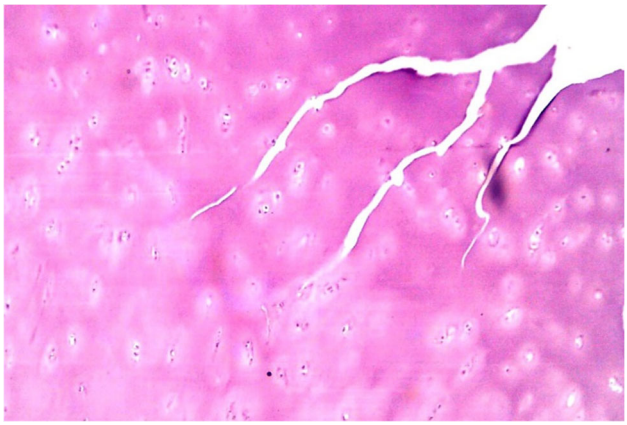

Figure 8 – ***Area of articular cartilage with numerous microcracks. HE staining, ×200.***

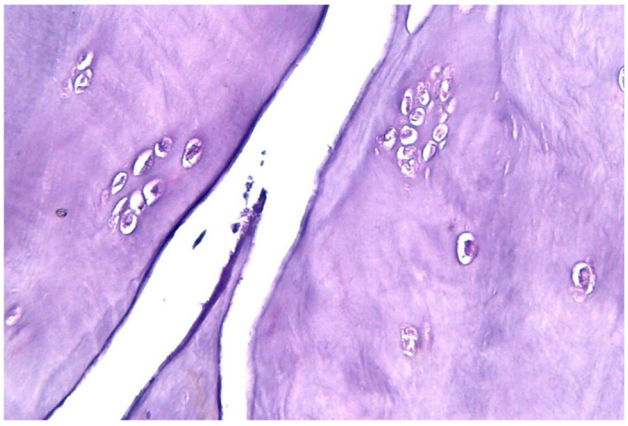

Figure 9 – ***Senescent chondrocytes, arranged in nests, unevenly distributed in the cartilaginous matrix. HE staining, ×200.***

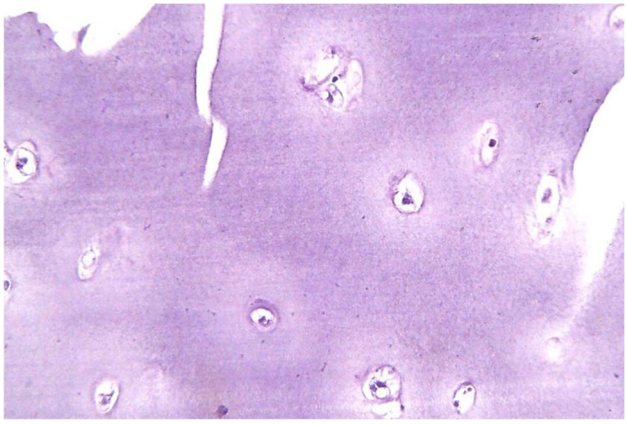

Figure 10 – ***Fragment of hyaline articular cartilage, with tears and cracks, with rare chondrocytes, with altered metabolism unable to synthesize and secrete conjunctive matrix in the chondroid globule. HE staining, ×400.***

Discussions

The objective of our study was to evaluate the efficacy of combining oral NSAIDs, a pharmacological treatment, with physical therapy methods, a non-pharmacological treatment, in alleviating knee pain and improving functional abilities in everyday activities. The study is limited by the small sample size and the subjective nature of each patient's pain threshold. However, the primary weakness of this study is the absence of a control group.

From a clinical point of view, the knee represents the most frequent site of OA [4]. Various guidelines that have tried to standardize and recommend treatments like the *ACR*, *OARSI*, *European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases* (ESCEO), *AAOS* and others exist [22–25]. The majority of these agree upon the combined use of pharmacological and non-pharmacological treatment options, while the last resort is represented by surgical intervention.

Even though oral NSAIDs represent in general a universal recommendation for pain management in OA, they carry a risk of GI, cardiovascular and renal side effects because they act on cyclooxygenase (COX)-enzymes, which can be found in the gastric lining, kidney, blood vessels and other tissues [26].

A narrative review by Tieppo Francio *et al.* (2017), comparing the oral inexpensive Diclofenac sodium with the more expensive topical presentation, but less prone to the systemic side effects of the drug, concluded that the first line of pharmacological management in OA should be the combination of Acetaminophen and Glucosamine/ Chondroitin sulfate with topical NSAIDs. But it should be taken into consideration that in otherwise healthy individuals the use of oral NSAIDs appears to be a safe and cost-effective solution [27].

In a meta-analysis conducted by da Costa *et al.* (2021), which included 192 trials, with the objective to evaluate the safety and efficacy of various types and doses of NSAIDs, opioids, and Acetaminophen in treating knee and hip OA, the findings revealed that Etoricoxib 60 mg/day and Diclofenac 150 mg/day were the most effective oral NSAIDs in alleviating both pain and improving function. The study concluded that when considering long-term daily use and patients with comorbidities, it is important to consider the risk of adverse events. The study also recommended that topical diclofenac at a dosage of 70–81 mg/day should be considered as the primary treatment option for KOA due to its lower systemic exposure and lower dosage [28].

Another meta-analysis by Bannuru *et al.* (2015), comparing the effectiveness of pharmacological interventions for OA of the knee, comprising of 137 studies found intra-articular treatments superior to NSAIDs, but otherwise all treatments showed clinically significant improvements with the exception of acetaminophen [29].

The use of electrotherapy in OA is largely inconclusive. A meta-analysis by Wu *et al.* consisting of 29 studies showed that TENS could significantly improve pain, dysfunction and walking ability in people with KOA, but is not effective regarding stiffness [30]. On the other hand, a double-blind, placebo-controlled trial by Reichenbach *et al.* between TENS and placebo found no improvement in KOA pain in any of the two groups [31].

Regarding therapeutic US, a study by Yeğin *et al.* (2017), involving 62 patients with KOA, concluded that both pain and function improve in the short term but do not persist in the long term [32]. In a meta-analysis conducted by Zeng *et al.*, 12 trials were examined to compare the effectiveness of pulsed US therapy and continuous US therapy. The results showed that pulsed US was more effective in reducing pain and improving function when compared to the control group. On the other hand, continuous US therapy only showed significant pain relief compared to the control group [33].

A randomized controlled trial by Robbins *et al.* consisting of 215 patients with KOA assessed the effectiveness of LLLT in combination with static stretching exercises on knee pain and functionality. Both laser therapy only group and laser plus stretching showed improvement regarding pain and disability [34].

Stausholm *et al.* conducted a meta-analysis of 22 randomized placebo-controlled trials and found that LLLT effectively reduces pain and impairment in individuals with KOA [35].

Ahmad *et al.* performed a systematic review and meta-analysis encompassing 10 studies, found that both LLLT and high-intensity laser therapy associated with rehabilitation exercises are beneficial in reducing KOA symptomatology [36]. Another meta-analysis that included nine random-controlled trials by Huang *et al.* found no significant difference between LLLT and control [37].

Thyroid gland dysfunctions have a longstanding association with musculoskeletal problems. A study conducted by Chen *et al.*, involving 8478 individuals, revealed that individuals with OA exhibited elevated levels of thyrotroph thyroxine resistance index (TT_4RI), thyroid-stimulating hormone (TSH), and thyroid feedback quantile-based index (TFQI). Additionally, they displayed lower levels of free triiodothyronine (fT_3) and free thyroxine (fT_4) compared to individuals without OA [38].

Another study by Kim *et al.* consisting of 109 patients with thyroid diseases used MSUS to assess the patients' joints. The results concluded that patients with both hyperthyroid and hypothyroid states were more frequently associated with MSUS abnormalities and knee pain than patients with an euthyroid state [39]. These last two studies showed a connection between the thyroid gland and OA, something that we also saw in our study, with more than half (56.53%) of the patients presenting thyroid disorders.

Conclusions

Our study monitored the evolution of the WOMAC, KOS–ADL, OKS scores and of the VAS in a group of patients with KOA. The treatment combination of physical therapy modalities and NSAIDs (Diclofenac) suggests a positive effect in reducing pain and improving function at the end of the 24-week period. While the beneficial effects of oral NSAIDs are undeniable, the risk of side-effects should be taken into consideration. Even though the effectiveness of TENS, LLLT and therapeutic US are inconclusive in literature, the combination of both pharmacological and non-pharmacological treatment is recommended by different Societies. While there are no disease-modifying drugs yet available, if no symptomatic treatment is efficient, surgical

interventions represent the final recommendation, such as in the case of our patients in the 24-week follow-up period. Future studies should ideally include a control group for a better comparison and validation of the treatment's effectiveness. Additional research is required to validate or refute the findings due to the limited number of participants and the absence of a control group.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (Approval No. 98/10.05.2023).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflict of interests

The authors declare no conflict of interests.

References

[1] Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage, 2013, 21(1):16–21. https://doi.org/10.1016/j.joca.2012.11.012 PMID: 23194896

[2] Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect, 1998, 47:487–504. PMID: 9571450

[3] Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, Bridgett L, Williams S, Guillemin F, Hill CL, Laslett LL, Jones G, Cicuttini F, Osborne R, Vos T, Buchbinder R, Woolf A, March L. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis, 2014, 73(7):1323–1330. https://doi.org/10.1136/annrheumdis-2013-204763 PMID: 24553908

[4] Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet, 2019, 393(10182):1745–1759. https://doi.org/10.1016/S0140-6736(19)30417-9 PMID: 31034380

[5] Sandell LJ. Etiology of osteoarthritis: genetics and synovial joint development. Nat Rev Rheumatol, 2012, 8(2):77–89. https://doi.org/10.1038/nrrheum.2011.199 PMID: 22231237

[6] Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation – United States, 2010–2012. MMWR Morb Mortal Wkly Rep, 2013, 62(44):869–873. PMID: 24196662 PMCID: PMC4585589

[7] Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med, 2016, 59(5–6):333–339. https://doi.org/10.1016/j.rehab.2016.07.004 PMID: 27546496

[8] Teichtahl AJ, Wluka AE, Proietto J, Cicuttini FM. Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects. Med Hypotheses, 2005, 65(2):312–315. https://doi.org/10.1016/j.mehy.2005.02.026 PMID: 15922106

[9] Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. Ann Phys Rehabil Med, 2016, 59(3):161–169. https://doi.org/10.1016/j.rehab.2015.12.003 PMID: 26797169

[10] Oo WM, Linklater JM, Hunter DJ. Imaging in knee osteoarthritis. Curr Opin Rheumatol, 2017, 29(1):86–95. https://doi.org/10.1097/BOR.0000000000000350 PMID: 27755179

[11] Hayashi D, Roemer FW, Guermazi A. Recent advances in research imaging of osteoarthritis with focus on MRI, ultrasound and hybrid imaging. Clin Exp Rheumatol, 2018, 36(5 Suppl 114): 43–52. PMID: 30296984

[12] Cioroianu GO, Florescu A, Muşetescu AE, Sas TN, Rogoveanu OC. Colchicine *versus* physical therapy in knee osteoarthritis. Life (Basel), 2022, 12(9):1297. https://doi.org/10.3390/life12091297 PMID: 36143334 PMCID: PMC9500941

[13] Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int, 2010, 107(9):152–162. https://doi.org/10.3238/arztebl.2010.0152 PMID: 20305774 PMCID: PMC2841860

[14] Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, Shiu KW, Ho T. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J, 2019, 25(2):127–133. https://doi.org/10.12809/hkmj187600 PMID: 30919810

[15] Jang S, Lee K, Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci, 2021, 22(5):2619. https://doi.org/10.3390/ijms22052619 PMID: 33807695 PMCID: PMC7961389

[16] Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). Arthritis Care Res (Hoboken), 2011, 63(Suppl 11):S208–S228. https://doi.org/10.1002/acr.20632 PMID: 22588746 PMCID: PMC4336550

[17] Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren–Lawrence classification of osteoarthritis. Clin Orthop Relat Res, 2016, 474(8):1886–1893. https://doi.org/10.1007/s11999-016-4732-4 PMID: 26872913 PMCID: PMC4925407

[18] Schmitz N, Laverty S, Kraus VB, Aigner T. Basic methods in histopathology of joint tissues. Osteoarthritis Cartilage, 2010, 18(Suppl 3):S113–S116. https://doi.org/10.1016/j.joca.2010.05.026 PMID: 20864017

[19] Takaku Y, Murai K, Ukai T, Ito S, Kokubo M, Satoh M, Kobayashi E, Yamato M, Okano T, Takeuchi M, Mochida J, Sato M. *In vivo* cell tracking by bioluminescence imaging after transplantation of bioengineered cell sheets to the knee joint. Biomaterials, 2014, 35(7):2199–2206. https://doi.org/10.1016/j.biomaterials.2013.11.071 PMID: 24360579

[20] Henson FMD, Vincent TA. Alterations in the vimentin cytoskeleton in response to single impact load in an *in vitro* model of cartilage damage in the rat. BMC Musculoskelet Disord, 2008, 9:94. https://doi.org/10.1186/1471-2474-9-94 PMID: 18577232 PMCID: PMC2443134

[21] Pritzker KPH, Gay S, Jimenez SA, Ostergaard K, Pelletier JP, Revell PA, Salter D, van den Berg WB. Osteoarthritis cartilage histopathology: grading and staging. Osteoarthritis Cartilage, 2006, 14(1):13–29. https://doi.org/10.1016/j.joca.2005.07.014 PMID: 16242352

[22] Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rheumatol, 2020, 72(2):220–233. https://doi.org/10.1002/art.41142 PMID: 31908163 PMCID: PMC10518852

[23] McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM, Underwood M. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage, 2014, 22(3):363–388. https://doi.org/10.1016/j.joca.2014.01.003 PMID: 24462672

[24] Bruyère O, Honvo G, Veronese N, Arden NK, Branco J, Curtis EM, Al-Daghri NM, Herrero-Beaumont G, Martel-Pelletier J, Pelletier JP, Rannou F, Rizzoli R, Roth R, Uebelhart D, Cooper C, Reginster JY. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum, 2019, 49(3):337–350. https://doi.org/10.1016/j.semarthrit.2019.04.008 PMID: 31126594

[25] Jevsevar DS, Brown GA, Jones DL, Matzkin EG, Manner PA, Mooar P, Schousboe JT, Stovitz S, Sanders JO, Bozic KJ, Goldberg MJ, Martin WR 3rd, Cummins DS, Donnelly P, Woznica A, Gross L; American Academy of Orthopaedic Surgeons. The American Academy of Orthopaedic Surgeons evidence-based guideline on: Treatment of osteoarthritis of the knee, 2nd edition. J Bone Joint Surg Am, 2013, 95(20):1885–1886. https://doi.org/10.2106/00004623-201310160-00010 PMID: 24288804

[26] Cooper C, Chapurlat R, Al-Daghri N, Herrero-Beaumont G, Bruyère O, Rannou F, Roth R, Uebelhart D, Reginster JY. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? Drugs Aging, 2019, 36(Suppl 1):15–24. https://doi.org/10.1007/s40266-019-00660-1 PMID: 31073921 PMCID: PMC6509083

[27] Tieppo Francio V, Davani S, Towery C, Brown TL. Oral *versus* topical Diclofenac sodium in the treatment of osteoarthritis. J Pain Palliat Care Pharmacother, 2017, 31(2):113–120. https://doi.org/10.1080/15360288.2017.1301616 PMID: 28388238

[28] da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, Bobos P, Gao L, Kiyomoto HD, Montezuma T, Almeida MO, Cheng PS, Hincapié CA, Hari R, Sutton AJ, Tugwell P, Hawker GA, Jüni P. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ, 2021, 375:n2321. https://doi.org/10.1136/bmj.n2321 PMID: 34642179 PMCID: PMC8506236

[29] Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med, 2015, 162(1):46–54. https://doi.org/10.7326/M14-1231 PMID: 25560713

[30] Wu Y, Zhu F, Chen W, Zhang M. Effects of transcutaneous electrical nerve stimulation (TENS) in people with knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil, 2022, 36(4):472–485. https://doi.org/10.1177/02692155211065636 PMID: 34971318

[31] Reichenbach S, Jüni P, Hincapié CA, Schneider C, Meli DN, Schürch R, Streit S, Lucas C, Mebes C, Rutjes AWS, da Costa BR. Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRELKA randomized clinical trial. Osteoarthritis Cartilage, 2022, 30(3):426–435. https://doi.org/10.1016/j.joca.2021.10.015 PMID: 34826572

[32] Yeğin T, Altan L, Kasapoğlu Aksoy M. The effect of therapeutic ultrasound on pain and physical function in patients with knee osteoarthritis. Ultrasound Med Biol, 2017, 43(1):187–194. https://doi.org/10.1016/j.ultrasmedbio.2016.08.035 PMID: 27727020

[33] Zeng C, Li H, Yang T, Deng ZH, Yang Y, Zhang Y, Ding X, Lei GH. Effectiveness of continuous and pulsed ultrasound for the management of knee osteoarthritis: a systematic review and network meta-analysis. Osteoarthritis Cartilage, 2014, 22(8):1090–1099. https://doi.org/10.1016/j.joca.2014.06.028 PMID: 24999112

[34] Robbins SR, Alfredo PP, Junior WS, Marques AP. Low-level laser therapy and static stretching exercises for patients with knee osteoarthritis: a randomised controlled trial. Clin Rehabil, 2022, 36(2):204–213. https://doi.org/10.1177/02692155211047017 PMID: 34714175

[35] Stausholm MB, Naterstad IF, Joensen J, Lopes-Martins RÁB, Sæbø H, Lund H, Fersum KV, Bjordal JM. Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials. BMJ Open, 2019, 9(10):e031142. https://doi.org/10.1136/bmjopen-2019-031142 PMID: 31662383 PMCID: PMC6830679

[36] Ahmad MA, A Hamid MSA, Yusof A. Effects of low-level and high-intensity laser therapy as adjunctive to rehabilitation exercise on pain, stiffness and function in knee osteoarthritis: a systematic review and meta-analysis. Physiotherapy, 2022, 114:85–95. https://doi.org/10.1016/j.physio.2021.03.011 PMID: 34654554

[37] Huang Z, Chen J, Ma J, Shen B, Pei F, Kraus VB. Effectiveness of low-level laser therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage, 2015, 23(9):1437–1444. https://doi.org/10.1016/j.joca.2015.04.005 PMID: 25914044 PMCID: PMC4814167

[38] Chen S, Sun X, Zhou G, Jin J, Li Z. Association between sensitivity to thyroid hormone indices and the risk of osteoarthritis: an NHANES study. Eur J Med Res, 2022, 27(1):114. https://doi.org/10.1186/s40001-022-00749-1 PMID: 35820977 PMCID: PMC9275280

[39] Kim BY, Kim SS, Park HK, Kim HS. Assessment of the relationship between knee ultrasound and clinical symptoms in patients with thyroid dysfunction. J Int Med Res, 2020, 48(1):300060519897701. https://doi.org/10.1177/0300060519897701 PMID: 31948293 PMCID: PMC7113714

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