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Effect of hydrocortisone ultrasonic phonophoresis in the treatment of knee osteoarthritis

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Abstract: (1) Background: Knee Osteoarthritis (KOA) is a frequent type of degenerative joint disease, which results in a gradual loss of function, discomfort, and stiffness. KOA can be effectively treated with oral drugs such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs may raise the dangers of renal, gastrointestinal, and other systemic toxicities. Compared with oral NSAIDs, topical gels are an alternative therapeutic option with fewer side effects, with less therapeutic efficacy. Studies on ultrasound (US) as a therapeutic method go back a long time in KOA. US not only relieves symptoms but may also provide potential cartilage repair effects, and regulates inflammatory responses. Widely used as a physical enhancer of drug absorption is ultrasonic phonophoresis. By making the skin more permeable to topical pharmaceuticals, it improves the absorption of drugs used topically. (2) Material and method: A monocentric study was conducted in the Center of Physical Therapy and Rehabilitation - "Dunărea de Jos" University of Galați on 20 patients, diagnosed with bilateral and unilateral moderate KOA. The experimental group (EG) included 10 patients who received 10 sessions of PT (Physical Therapy), transcutaneous electrical nerve stimulation (TENS), and Ultrasound (US) phonophoresis therapy with hydrocortisone 10mg/g. The control group (CG) included 10 patients who received 10 sessions of TENS and US with neutral gel. (3) Results: All patients were clinically assessed with The "timed up and go test" (TUG), pain scale (VAS), and WOMAC. The *t*-test was used to calculate the statistical differences between the means of the EG and CG. (4) Conclusion: Hydrocortisone therapy combined with PT had a beneficial effect on pain and functional mobility in patients with KOA form EG. Furthermore, significantly greater improvement was observed among the intervention group with hydrocortisone.

Keywords: knee osteoarthritis; recovery; ultrasonic phonophoresis; physical therapy; dexamethasone.

1. Introduction

Osteoarthritis (OA) is a frequent type of degenerative joint disease. The main peripheral joint affected is the knee, which results in a gradual loss of function, discomfort, and stiffness [1]. One of the main causes of disability worldwide is OA of the hip and knee [2]. About 9000 knee arthroplasties are performed each year in England and Wales due to knee OA (KOA), which is a leading source of pain and disability in older people [3].

Clinically, patients with KOA exhibit symptoms such as pain, stiffness, and functional limitations linked to knee swelling and effusion, which may have an adverse effect on their quality of life (4). Exercises that target the heart and the muscles can help with KOA. Aerobic walking has been demonstrated to reduce pain in three RCTs [5,6].

Mündermann et al. and Chang et al. have shown that weak hip abductors diminish propulsion or explosive force during weight-bearing exercises, which in turn pressures the medial tibiofemoral joint and advances illness [7,8].

Hip abductor strengthening and KOA were found to be positively correlated in the current research and meta-analysis. The functional scores improved and the level of pain was somewhat reduced as a result of strengthening the hip abductors. These encouraging results imply that hip abductor strengthening can be employed as an efficient training program in individuals with KOA, but additional research is needed to determine whether these advantages on the evaluated functional outcomes are sustained over the long term. We now have a better grasp of the role, significance, and influence of hip abductor strengthening in patients with knee osteoarthritis according to the results of this review [9]. Ultrasonic phonophoresis uses sound waves to penetrate soft tissues to penetrate and absorb the skin to deliver therapeutic drugs [10].

Widely used as a physical enhancer of drug absorption by ultrasonic waves is ultrasonic phonophoresis. By making the skin more permeable to topical pharmaceuticals, it improves the absorption of drugs used topically. Similar to how ultrasound is applied, phonophoresis does the same thing, except the coupling agent is changed to include a drug [11,12].In physical therapy, phonophoresis has long been a standard, according to Gurney, hydrocortisone acetate is the substance used in ultrasonic phonophoresis the most frequently [13].

KOA is a chronic, degenerative condition that typically affects middle-aged or older people and is a major contributor to disability in the adult population [14,15]. The diverse pathophysiology of KOA is defined by its complex and multifaceted nature. It has been hypothesized that these variations result from the existence-presence of underlying phenotypes indicative of various disease processes [16,17].

Although it is more prevalent in older people, KOA is a condition that is not always associated with aging. The prevalence of KOA has increased as the global population ages, and the percentage of people aged over 60 is increasing [18,19]. Statistically, KOA is the most prevalent form (6% of all adults), men aged 60-64 years are more likely to have osteoarthritis in the right knee (23%) than in the left knee (16.3%), although women appear to have a more even distribution in the right knee, 24.2%, and in the left knee, 24.7% [20,21,22,23].

Only 15% of people with radiologically proven KOA report knee pain, despite the presence of typical radiological markers of the condition. Because of insufficient clinical trials addressing specific features of rehabilitative treatment modalities, current guidelines on conservative treatment of KOA are peppered with consensus recommendations that are not convincing [24,25,26[. Patients with KOA are advised to engage in self-management, weight-reduction, programs of muscle strengthening, low-impact aerobic exercise, neuromuscular treatment, and physical activity [27,28].

KOA can be effectively treated with oral pharmaceuticals such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) [29,30]. However, oral NSAIDs may raise the dangers of renal, gastrointestinal, and other systemic toxicities. Compared with oral

NSAIDs, topical gels are an alternative therapeutic option with fewer side effects, with less therapeutic efficacy [31,32].

Studies on ultrasound as a therapeutic method go back a long time [33]. Through the absorption of mechanical energy and the generation of heat in tissues, ultrasound has a therapeutic effect [34]. Ultrasound (US) therapy is a non-invasive and safe form of physical therapy (PT) used for musculoskeletal conditions, including KOA. The US not only relieves symptoms but may also provide potential cartilage repair effects [35]. Several studies have shown that the US promotes collagen formation, regulates inflammatory responses, and induces cartilage repair [36,37].

Widely used as a physical enhancer of drug absorption is ultrasonic phonophoresis. By making the skin more permeable to topical pharmaceuticals, it improves the absorption of drugs used topically. Similar to how ultrasound is applied, ultrasonic phonophoresis does the same thing, except the coupling agent is changed to include a drug [38,39].

TENS reduces pain in KOA by selectively stimulating large diameter, low threshold, non-nociceptive afferents in the dermis and by increasing motor neuron excitability of the quadriceps muscle. Transcutaneous electrical nerve stimulation (TENS) is a method used worldwide by physicians and physiotherapists in the treatment of pain symptoms [40].

To limit the loss of joint function caused by KOA it is necessary to implement specific physiotherapy exercises (PTE) to relieve KOA pain, but also to slow down the progression of this condition. In the literature, the importance and effectiveness of individualizing regularly performed exercises that maintain joint mobility, prevent joint cartilage degradation and prevent muscle atrophy are emphasized, thus improving joint stability and coordination in patients with KOA. Most clinical guidelines recommend PTE, weight loss, and patient education in the rehabilitation of KOA [41,42].

2. Materials and Methods

The research aims to design and implement a rehabilitation scheme consisting of physiotherapy procedures to improve pain perception and decrease joint stiffness in the knee and improve daily activities.

2.1. Trial Procedure

The study was conducted from 11 October 2022 until 11 December 2022, treatment was provided in the Center of Physical Therapy and Rehabilitation - "Dunărea de Jos" University of Galați.

The study complied with international conventions on the processing of personal data and ensuring the anonymity of the patients following the Helsinki Declaration of Ethical Principles. The Ethics Committee of the higher education institution gave its consent to the research with number 12 dated 24.09.2022.

The study was performed on a group of 20 patients , diagnosed with bilateral and unilateral KOA (14 men and 6 women) in stage 2 of the "Kellgren and Lawrence system" (KL) based on radiological examination of the anterior-posterior view of an X-ray of the knee. KL classification is commonly used in epidemiological research studies of KOA to guide health professionals in their clinical decision-making, especially for managing patients with surgical indications. The KL system uses five classes: KL 0 (normal), KL 1 (narrowing of the joint space), KL 2 (osteophytes and narrowing of the joint space), KL 3 (multiple osteophytes, well-defined joint narrowing, sclerosis, and possible bone deformity), and KL 4 (large osteophytes, marked joint narrowing, severe sclerosis, and defined bone deformity) [43].

2.2 Study Design

Out of a total of 35 patients diagnosed with KOA, and the resulting inclusion and exclusion citations from the study, only 20 who were eligible for this experimental study were divided into 2 groups.

For the inclusion criteria, the eligible patients were those diagnosed and confirmed with KOA radiologically with KL 2 stage without previous, and patients who had not undergone any surgery or physical therapy (PT) procedure in the last 6 months. Patients with bilateral KL 2 stage KOA were also included but only if they had a single symptomatic knee and did not have increased inflammatory markers above the accepted values (erythrocyte sedimentation rate, rheumatoid factors, normal blood count, C-reactive protein, and fibrinogen).

The exclusion criteria included whether they had acute rheumatological conditions, autoimmune diseases, KOA stage 3/4 of the "Kellgren and Lawrence system", lower limb thrombosis, and arteriopathy. Balance disorders, neuropathies/sensory disorders, or skin lesions around the knee were other exclusion criteria in this study. Patients were also excluded if they had contraindications or precautions for the use of corticosteroids were not included in the study.

2.3 Patients

The experimental group (EG) included 10 patients (7 males and 3 females) who received 10 sessions of PT, transcutaneous electrical nerve stimulation (TENS) and Ultrasound (US) phonophoresis therapy with hydrocortisone 10mg/g. Three having bilateral KOA, four having left KOA, and three patients having right KOA, with the following characteristics: age 56+8, height 1.60cm+0.10, weight 82kg+0.15 and BMI (body index mass) 31.6 + 5.

Control group (CG) included 10 patients (men and 3 women) received 10 sessions of TENS and US with neutral gel. Two having bilateral KOA, six having left KOA, and four patients having right KOA, with the following characteristics: age 61+7, height 1.70cm+0.10, weight 80kg+14 and BMI 28.24 + 6.96.

2.4 Physiotherapy (PT)

PT1 for EG and EC - electrotherapy-conventional TENS electroanalgesia for 30 minutes min using two frequency channels at 80 Hz and 100 μs, biphasic.

PT2-US: EG = 6 min of 0.4-0.5 W/cm2 at 1 MHz with a 30% duty cycle with hydrocortisone; EC = 6 min of 0.4-0.5 W/cm2 at 1 MHz with a 30% duty cycle with neutral gel

PTE3-EG and EC: between 50 min per session with moderate-intensity exercise that included the following: warm up for 10 min with a stationary bike, static quads with a hold for 7 s, knee extensions over a roll with a hold for 7 s, single-leg raises for 30 reps, step-ups for 30 reps, calf raises for three sets of 10-15, and wall squats with a hold for 10 s. Neuro-proprioceptive facilitation techniques were used in four movement patterns repeated 2-3 times as a set: (flexion-abduction-internal), (extension-adduction-external), (flexion-adduction-external), and (extension-abduction-internal) rotations. The Neuro-proprioceptive facilitation techniques included (contract-relax), (hold-relax); (reversal of antagonists), and (repeated stretch) [44]. The dosage consisted of three sets of ten repetitions, with each patients' starting weight matched to their maximal weight for ten repetitions.

2.5. Assessment Tests and Outcomes

All results were analyzed from the perspective of multiple indicators: the visual analog scale (VAS), the WOMAC scale, and Timed Up & Go Test (TUG)

This pain perception assessment tool, called VAS, is used worldwide by physiotherapists and clinicians (45). The VAS is scored on a scale of 0 to 10, with 0 representing no pain and 10 representing extreme pain perception [46].

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is used to assess KOA. Pain, stiffness, and function are part of three subscales of The WOMAC self-administered questionnaire. The maximum WOMAC score is 96 and is a patient-made assessment that addresses activities of daily living, functional mobility, walking, general health, and quality of life. A high WOMAC score correlates with decreased quality of life [47].

The TUG test counts the number of seconds needed for a person to get out of a regular armchair, move three meters, turn around, and return to the chair before sitting down once more. The patient uses an assistive device if necessary and walks safely while wearing appropriate footwear.

3. Results

The study included 20 participants divided into two groups. The first group was treated with hydrocortisone (group A) and the second one without (group B). Each group was assessed before the intervention and after the intervention. The study included 14 male participants (70%) and 6 female participants (30%). Figure 1 shows gender and body mass index (BMI) distributions according to the study group. The mean age among study participants was 58.8 $\pm$ 80.6 years with a median age of 60 years. Age ranged from 42 to 70 years. Table 1 shows characteristics and anthropometric measurements of participants according to the study group. As indicated by the independent *t*-test, no significant differences ($P > 0.05$) were observed in the mean values for age, weight, or height between the two tested groups.

Table 1: Summary of the physical characteristics of both patient groups

Item	Group A	Group B	*t*	P value
Age (mean $\pm$ SD)	56 $\pm$ 8	61 $\pm$ 7	-1.424	0.172
Weight (mean $\pm$ SD)	82 $\pm$ 15	80 $\pm$ 14	0.312	0.759
Height (mean $\pm$ SD)	1.6 $\pm$ 0.1	1.7 $\pm$ 0.1	-1.588	0.130
BMI (mean $\pm$ SD)	31.6 $\pm$ 5	28.24 $\pm$ 6.96	1.239	0.231

The statistical analysis using the 2 × 2 mixed-design MANOVA indicated significant effects of the treatment (the first independent variable) on all tested dependent variables (the VAS, TUG, and WOMAC subscales) for the two groups. Similarly, significant effects were observed for the measurement times (the second independent variable) on the tested dependent variables. In addition, the interaction between the two independent variables was significant (table 2), which indicated that the effect of the treatment (first independent variable) on the dependent variables was influenced by the measurement time (second independent variable).

Table 2: The 2×2 mixed-design multivariate analysis of variance (MANOVA) for all dependent variables between the two groups at different measurement times

Source of variation	F	P
Groups	2.38	0.015*
Measurement times	60.543	0.0001*
Interaction	16.26	0.0001*

The within-groups comparison revealed a significant posttreatment reduction in all measurement assessment compared to the pretreatment scores for both groups (table 3). The intervention group had a 70.56%–75.05% improvement in pain intensity (VAS and pain subscale of WOMAC, respectively) compared to 35.8%–40.64% for the control group.

Table 3: Summary of the pre-treatment and post-treatment mean ± SD and P values of the outcome measures for both groups

Outcome measures		Group A	Group B	P (betweengroups)
		Mean ± SD	Mean ± SD	
VAS	Pre-treatment	4.9 + 2.47**	7.1 + 1.28	
	Post-treatment	1.4 + 1.35**	4.8 + 1.47	
TUG	Pre-treatment	12.35 + 1.32**	14.2 + 1.46**	
	Post-treatment	10.33 + 1.5**	13.17 + 1.77**	
WOMAC pain	Pre-treatment	10.4 + 4.27**	14.6 + 3.13	
	Post-treatment	2.9 + 2.13**	8.9 + 2.23	
WOMAC stiffness	Pre-treatment	5.3 + 1.56	6.6 + 1.5	
	Post-treatment	1.6 + 1.26	4.2 + 1.22	
WOMAC function	Pre-treatment	38 + 10.14	44 + 6.79	
	Post-treatment	13.5 + 6.32	32.5 + 6.18	
WOMAC total	Pre-treatment	35.7 + 15.62**	64.5 + 11.32**	
	Post-treatment	18 + 8.51**	45.6 + 7.3**	

*Significance level is set at an alpha level of <0.05. SD: standard deviation. P: Probability value.
**Statistically significant difference from the pre-treatment value for the same group.

The TUG test and stiffness and physical function subscales of the WOMAC were significantly improved posttreatment compared to the pretreatment values for both groups (multiple pairwise post hoc comparison tests used for all). Functional mobility likewise showed a higher rate of improvement in the intervention group compared to control (57.69% vs. 27.48% for TUG [MD:
−2.83; CI: −4.38– −1.28] and 53.24vs. 22.97 [MD: −2.6; CI: −3.77– −1.42] and 56.1 vs. 26.42% [MD: −19; CI: −24.88– −13.12] for the joint stiffness and physical function subscales of the WOMAC, respectively). Significant differences were observed for the posttreatment mean values for all outcome measures between the two groups, favoring group A. A comparison of the mean pretreatment values showed no significant differences between the two groups.

A significant reduction in the total WOMAC score was observed after treatment compared to the pretreatment value for both groups (paired t-test). An unpaired t-test revealed that the mean values of the VAS, TUG, and WOMAC pain subscale were significant between groups at the pretreatment measurements. On the other hand, other

parameters were not significantly different between the two groups before treatment. However, significant differences were found in the mean values after treatment between the two groups, which favored group A. The rate of improvement of the total WOMAC after treatment was 56.43% for Group A compared to 29.68% for Group B (MD: −27.6; CI: −35.05– −20.14).

Both treatment groups demonstrated a clinically significant improvement in function. Whereas the intervention group reached a clinically significant effect size (−2.69). Direct comparison of both the groups showed a clinically significant pain reduction and improvement in function in favor of the intervention group (effect size −1.4 and −2.01, respectively).

4. Discussions

This study used PROMs and objective functional tests to document the effects of dexamethasone coupled with ultrasonic phonophoresis. Our findings show that in patients with mild-to-moderate knee OA, DxPh had a favorable impact on pain and function. Following the treatment, both groups showed improvements in function (TUG test, stiffness, and physical function subscales of the WOMAC, and the total WOMAC) as well as pain (VAS and the pain subscale of the WOMAC). The ultrasonic phonophoresis group, however, saw a noticeably bigger improvement. In order to prevent gender-related variations in the execution of the functional evaluation, the study was restricted to female patients.

For the treatment to be successful, the medication choice for ultrasonic phonophoresis appears to be just as crucial as the ultrasonic parameters (Table 3). The use of ultrasound facilitation was shown to result in a higher buildup of dexamethasone in the serum when compared to sham ultrasound used over an occlusive bandage.

This study was restricted to contrasting the immediate effects of ultrasonic therapy and DxPh. The study's follow-up duration, however, complies with the requirements for inclusion in a recent network meta-analysis of the best available research for the nonsurgical treatment of KOA.

5. Conclusions

Our results showed that hydrocortisone therapy combined with PT had a beneficial effect on pain and functional mobility in patients with KOA. Furthermore, significantly greater improvement was observed among the intervention group with hydrocortisone.

PT 1+2 improved patients' quality of life but the best results from a clinical point of view were recorded by the ultrasonic phonophoresis group.

Limitations: the evaluation contained only 3 types of clinical tests, therefore studies would also require the use of ROM, muscle strength, and clinical tests such as patellar shock, J test, MRI, and musculoskeletal ultrasound to determine synovial membrane changes. Another weakness was the small number of subjects included in the study.

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References

1. Lawrence, R. C., Helmick, C. G., Arnett, F. C. et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis & Rheumatism: *Official Journal of the American College of Rheumatology*. **1998,** *41(5)*, 778-799. https://doi.org/10.1002/1529-0131
2. Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen et al. The globalburden of hip and knee osteoarthritis: estimates from the global burden of disease 2010study. *Annals of the rheumatic diseases*. **2014**, *73(7),* 1323-1330. http://dx.doi.org/10.1136/annrheumdis-2013-204763
3. Scally, G., Tackling teenage pregnancy in the UK. *The Lancet*. **1999**, *353(9171)*, 2178. https://doi.org/10.1016/S0140-6736(99)00208-1
4. Oliveira, A. M. I. D., Peccin, M. S., Silva, K. N. G. D., Teixeira, L. E. P. D. P., & Trevisani, V. F.M., Impact of exercise on the functional capacity and pain of patients with knee osteoarthritis: a randomized clinical trial. *Revista brasileira de reumatologia.* **2012**, *52*, 876-882. Available from: https://www.scielo.br/j/rbr/a/dBcJfq5HBqHskMmMrCZ7YKH/
5. Bautch, J. C., Malone, D. G., & Vailas, A. C., Effects of exercise on knee joints withosteoarthritis: a pilot study of biologic markers. *Arthritis & Rheumatism: Official Journalof the American College of Rheumatology*. **1997**, *10(1),* 48-55. https://doi.org/10.1002/art.1790100108
6. Kovar, P. A., Allegrante, J. P., MacKenzie, C. R., Peterson, M. G., Gutin, B., & Charlson, M.E., Supervised fitness walking in patients with osteoarthritis of the knee: a randomized,controlled trial. *Annals of internal medicine*, **1992**, *116(7),* 529-534. https://doi.org/10.7326/0003-4819-116-7-529
7. Mündermann, A., Dyrby, C. O., & Andriacchi, T. P., Secondary gait changes in patients withmedial compartment knee osteoarthritis: increased load at the ankle, knee, and hipduring walking. *Arthritis & rheumatism*. **2005**, *52(9)*, 2835-2844. https://doi.org/10.1002/art.21262
8. Chang, A., Hayes, K., Dunlop, D., Song, J., Hurwitz, D., Cahue, S., & Sharma, L., Hip abduction momentand protection against medial tibiofemoral osteoarthritis progression. *Arthritis & Rheumatism*. **2005**, *52(11)*, 3515-3519. https://doi.org/10.1002/art.21406
9. Thomas, D. T., Prabhakar, A. J., Dineshbhai, P. V., & Eapen, C., Hip abductor strengtheningin patients diagnosed with knee osteoarthritis–a systematic review and meta-analysis. *BMC Musculoskeletal Disorders*. **2022**, *23(1)*, 1-14. https://doi.org/10.1186/s12891-022-05557-6
10. Souza, J., Meira, A., Volpato, N. M., Mayorga, P., & Gottfried, C., Effect of phonophoresison skin permeation of commercial anti-inflammatory gels: sodium diclofenac andketoprofen. *Ultrasound in medicine & biology*. **2013**, *39(9),* 1623-1630. https://doi.org/10.1016/j.ultrasmedbio.2013.02.009
11. Gutenbrunner, C., Bender, T., Cantista, P., & Karagülle, Z., A proposal for a worldwidedefinition of healthresort medicine, balneology, medical hydrology andclimatology. *International Journal of Biometeorology*. **2010**, *54*, 495-507. https://doi.org/10.1007/s00484-010-0321-5
12. Polat, B. E., Hart, D., Langer, R., & Blankschtein, D., Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends. *Journal of controlled release.* **2011**, *152(3)*, 330-348. https://doi.org/10.1016/j.jconrel.2011.01.006
13. Gurney, A. B., Wascher, D., Schenck, R., Tennison, A., & Jaramillo, B., Absorption of hydrocortisone acetate in human connective tissue using phonophoresis. *Sports health*. **2011**, *3(4),* 346-351. https://doi.org/10.1177/1941738111405970
14. Salacinski, A. J., Krohn, K., Lewis, S. F., Holland, M. L., Ireland, K., & Marchetti, G., Theeffects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial. *journal of orthopaedic &sports physical therapy*. **2012**, *42(12)*, 985-995. https://www.jospt.org/doi/10.2519/jospt.2012.3813
15. Hunter, D. J., & Lo, G. H., The management of osteoarthritis: an overview and call to appropriate conservative treatment. *Rheumatic Disease Clinics of North America*. **2008**, *34*(3), 689-712. https://doi.org/10.1016/j.rdc.2008.05.008

16. Bierma-Zeinstra, S. M., & Verhagen, A. P., Osteoarthritis subpopulations and implicationsfor clinical trial design. *Arthritis research & therapy*. **2011**, *13*, 1-9. https://doi.org/10.1186/ar3299
17. Dell'Isola, A., Allan, R., Smith, S. L., Marreiros, S. S. P., & Steultjens, M., Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC musculoskeletal disorders*. **2016**, *17*(1), 1-12. https://doi.org/10.1186/s12891-016-1286-2
18. Lee, R., & Kean, W. F., Obesity and knee osteoarthritis. *Inflammopharmacology*. **2012**, *20*, 53-58. https://doi.org/10.1007/s10787-011-0118-0
19. Felson, D. T., Developments in the clinical understanding of osteoarthritis. *Arthritisresearch & therapy*. **2009**, *11*, 1-11. https://doi.org/10.1186/ar2531
20. Masouros, S. D., Bull, A. M. J., & Amis, A. A., Biomechanics of the knee joint. *Orthopaedicsand Trauma*. **2010**, *24*(2), 84-91. https://doi.org/10.1016/j.mporth.2010.03.005
21. Scanzello, C. R., & Goldring, S. R., The role of synovitis in osteoarthritis pathogenesis. *Bone*. **2012**, *51*(2), 249-257. https://doi.org/10.1016/j.bone.2012.02.012
22. Zaripova L, Tazhibayeva D, Kabdualieva N, Aitbayeva Z, Beglarova G, Yermentayeva L, et al. Osteoarthritis: A contemporary view of the problem, the possibilities of therapy and prospects for further research. *J CLIN MED KAZ.* **2022**, *19(6)* 6-12. https://doi.org/10.23950/jcmk/12629
23. D'Ambrosia RD., Epidemiology of osteoarthritis. *Orthopedics 28 (Suppl. 2)*. **2005**, 201– 205 https://doi.org/10.3928/0147-7447-20050202-04
24. Hannan, M. T., Felson, D. T., & Pincus, T. H. E. O. D. O. R. E., Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *The Journal ofrheumatology.* **2000**, 27(6), 1513-1517. https://www.altmetric.com/details/2779849
25. Jevsevar, D. S., Brown, G. A., Jones, D. L., Matzkin, E. G., Manner, P. A., Mooar, P., et al. The American Academy of Orthopaedic Surgeons evidence-based guideline on:treatment of osteoarthritis of the knee. *JBJS*. **2013**, *95*(20), 1885-1886.
26. Scott, J., Checketts, J. X., Horn, J. G., Cooper, C., & Vassar, M., Knee osteoarthritis and current research for evidence—are we on the right way?. *International Orthopaedics*. **2018**, *42*, 2105-2112. https://doi.org/10.1007/s00264-018-3932-9
27. Jevsevar, D. S., Treatment of osteoarthritis of the knee: evidence-based guideline. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons*. **2013,** *21*(9), 571-576 http://dx.doi.org/10.5435/JAAOS-21-09-571
28. Zhang, W., Nuki, G., Moskowitz, R. W., Abramson, S., Altman, R. D., Arden, N. K. et al. OARSI recommendations for the management of hip and knee osteoarthritis:part III: Changes in evidence following systematic cumulative update of researchpublished through January 2009. *Osteoarthritis and cartilage*. **2010**, *18*(4), 476-499. https://doi.org/10.1016/j.joca.2010.01.013
29. Jevsevar, D. S., Shores, P. B., Mullen, K., Schulte, D. M., Brown, G. A., & Cummins, D. S., Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons*. **2018**, *26*(9), 325-336. DOI: 10.5435/JAAOS-D-17-00318
30. Adatia, A., Rainsford, K. D., & Kean, W. F., Osteoarthritis of the knee and hip. Part II: therapy with ibuprofen and a review of clinical trials. *Journal of Pharmacy and Pharmacology*. **2012**, *64*(5), 626-636.https://doi.org/10.1111/j.2042-7158.2012.01456.x
31. Andrew Naylor, T., & Naylor, S., Distribution and risk factors for stress fractures incompetitive figure skaters and association with acute fractures. *The Physician andSportsmedicine*. **2021**, 1-5. DOI: 10.1080/00913847.2021.1981748
32. Rodriguez-Merchan, E. C., Topical therapies for knee osteoarthritis. *Postgraduatemedicine*, (2018). *130*(7), 607-612. https://doi.org/10.1080/00325481.2018.1505182
33. Baker, K. G., Robertson, V. J., & Duck, F. A., A review of therapeutic ultrasound: biophysicaleffects. *Physical therapy*. **2001**, *81*(7), 1351-1358. https://doi.org/10.1093/ptj/81.7.1351
34. Aiyer, R., Noori, S. A., Chang, K. V., Jung, B., Rasheed, A., Bansal, N., ... & Gulati, A., Therapeutic ultrasound for chronic pain management in joints: a systematic review. *PainMedicine*. **2020**, *21*(7), 1437-1448. https://doi.org/10.1093/pm/pnz102
35. Rothenberg, J.B.; Jayaram, P.; Naqvi, U.; Gober, J.; Malanga, G.A. The Role of Low-Intensity Pulsed Ultrasound on Cartilage Healing in Knee Osteoarthritis: A Review. *PM&R.* **2017**, *9*, 1268–1277.
36. Paliwal, S.; Mitragotri, S. Therapeutic Opportunities in Biological Responses of Ultrasound. *Ultrasonics* **2008**, *48*, 271–278.

37. Schumann, D.; Kujat, R.; Zellner, J.; Angele, M.K.; Nerlich, M.; Mayr, E.; Angele, P. Treatment of Human Mesenchymal Stem Cells with Pulsed Low Intensity Ultrasound Enhances the Chondrogenic Phenotype In Vitro. *Biorheology* **2006**, *43*, 431–443.
38. Gutenbrunner, C., Bender, T., Cantista, P., & Karagülle, Z., A proposal for a worldwidedefinition of healthresort medicine, balneology, medical hydrology andclimatology. *International Journal of Biometeorology***. 2010**, *54*, 495-507. https://doi.org/10.1007/s00484-010-0321-5
39. Polat, B. E., Hart, D., Langer, R., & Blankschtein, D., Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends. *Journal of controlled release*. **2011**, *152*(3), 330-348. https://doi.org/10.1016/j.jconrel.2011.01.006
40. Iijima, H.; Eguchi, R.; Shimoura, K.; Yamada, K.; Aoyama, T.; Takahashi, M. Transcutaneous Electrical Nerve Stimulation Improves Stair Climbing Capacity in People with Knee Osteoarthritis. *Sci. Rep*. **2020**, *10*, 7294.
41. Hou, Y.; Yang, Z.; Lin, J.; Chen, Y.; Xing, D.; Wang, B. Systematic Review of Clinical Practice Guidelines on Exercise Therapy for Knee Osteoarthritis and Critical Appraisal Using AGREEII Instrument. *Osteoarthr. Cartil.* **2018**, *26*, S324–S325.
42. Song, Q.; Shen, P.; Mao, M.; Sun, W.; Zhang, C.; Li, L. Proprioceptive neuromuscular facilitation improves pain and descending mechanics among elderly with knee osteoarthritis. *Scand. J. Med. Sci. Sports* **2020**, *30*, 1655–1663.
43. Noyes, F. *Noyes' Knee Disorders: Surgery, Rehabilitation, Clinical Outcomes*, 1st ed.; *Saunders: Philadelphia, PA, USA*, **2009,** ISBN 978-1-4377-2118-8.
44. Faiz, K.W. VAS—Visual Analog Scale. *Tidsskr. Nor. Laegeforen* **2014**, *134*, 323.
45. Alghadir, A.H.; Anwer, S.; Iqbal, A.; Iqbal, Z.A. Test-Retest Reliability, Validity, and Minimum Detectable Change of Visual Analog, Numerical Rating, and Verbal Rating Scales for Measurement of Osteoarthritic Knee Pain. *J. Pain Res.* **2018**, *11*, 851–856.
46. Silman, A.; Smolen, J.; Weinblatt, M.; Weisman, M.; Hochberg, M.; Gravallese, E. *Rheumatology, 2-Volume Set*, 7th ed.; Elsevier: Amsterdam, The Netherlands, **2018,** ISBN 978-0-7020-7306-9.
47. Said Ahmed, M. A., Boles Saweeres, E. S., Abdelkader, N. A., Abdelmajeed, S. F., & Fares, A. R., Improved Pain and Function in Knee Osteoarthritis with Dexamethasone Phonophoresis: A Randomized Controlled Trial. *Indian Journal of Orthopaedics*. **2019**, *53*(6), 700-707. https://doi.org/10.4103/ortho.IJOrtho_639_18