Non-pharmacological and non-surgical interventions for knee osteoarthritis: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of the present systematic review and meta-analysis is to know, based on the available randomized controlled trials (RCTs), if the non-surgical and non-pharmacological interventions commonly used for knee osteoarthritis (OA) patients are effective and which are the most effective ones.

Material and Methods: RCTs were identified through electronic databases respecting the following terms to guide the search strategy: PICO (*P*atients – Humans with knee OA; *I*ntervention – Non-surgical and non-pharmacological interventions; *C*omparison – Pharmacological, surgical, placebo, no intervention, or other non-pharmacological/non-surgical interventions; *O*utcomes – Pain, physical function and patient global assessment). The methodological quality of the selected publications was evaluated using the PEDro and GRADE scales. Additionally, a meta-analysis was performed using the RevMan. Only studies with similar control group, population characteristics, outcomes, instruments and follow-up, were compared in each analysis.

Results: Initially, 52 RCTs emerge however, after methodological analysis, only 39 had sufficient quality to be included. From those, only 5 studies meet the meta-analysis criteria. Exercise (especially resistance training) had the best positive effects on knee OA patients. Pulsed Electromagnetic Fields and Moxibustion showed to be the most promising interventions from the others. Balance Training, Diet, Diathermy, Hydrotherapy, High Level Laser Therapy, Interferential Current, Mudpack, Neuromuscular Electrical Stimulation, Musculoskeletal Manipulations, Shock Wave Therapy, Focal Muscle Vibration, stood out, however more studies are needed to fully recommend their use. Other interventions did not show to be effective or the results obtained were heterogeneous.

Conclusions: Exercise is the best intervention for knee OA patients. Pulsed Electromagnetic Fields and Moxibustion showed to be the most promising interventions from the others options available.

Keywords: Knee osteoarthritis; Non-surgical; Non-pharmacological; Interventions

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is a major contributor to functional and social impairment, disability, reduced independence and poorer quality-of-life in older adults[1-7]. There are at least 151,4 million persons worldwide suffering from this disease[8]. Yet, in nowadays these values are for sure higher, since the incidence of new cases is 200–250//100 000/year[9]. Moreover, there is an increasing need for urgent attention to this disease due to the societal trends in the population such as ageing, obesity prevalence and joint injury, estimating that the number of people affected by OA will increase about 50% over the next 20 years[5,10,11].

From all joint that can be affected by OA, the knee is the most prevalent (especially in elderly women), where a third of older adults in the general population shows radiological evidence of knee OA[11-16]. Current OA rehabilitation strategy is a complex process that uses surgical and non-surgical interventions (pharmacological and non-pharmacological)[5,9,14,17-20]. As the majority of the non-pharmacological and non-surgical interventions are safe, low cost, low tech, incorporate self-management performed at home or in the com-

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munity and have a substantial public health impact, they play a critical role in the patients' life as they are nowadays the first step in the knee OA management[5,9,14,17-20]. Due to their risks, complications and post-outcomes other strategies are a valid option for patients who failed to respond to these measures[5,14,17,19,20].

Although there are several studies, recommendations and guidelines for knee OA management, there is still poor adherence to these interventions by the patients and even by the health professionals. Due to this poor adherence, wide range of treatments and even uncertainty in some therapies, further research seems necessary to clarify which ones are the most efficient evidence-based non-pharmacological and non-surgical treatments to manage knee OA.

Therefore, the aim of the present systematic review and meta-analysis is to find out, based on the available randomized controlled trials, if the non-surgical and non-pharmacological interventions commonly used for knee OA patients are effective and which are the most effective ones.

#1 "Knee*" "Osteoarthr*" OR "Gonarthr*"

#2 elder* OR older* OR oldest OR aged

#3 "Humans"[Mesh]

#4 #2 OR #3

#5 ("Exercise"[Mesh] OR "Low-Level Light Therapy"[Mesh] OR "Transcutaneous Electric Nerve Stimulation"[Mesh] OR "Acupuncture Therapy"[Mesh] OR "Yoga"[Mesh] OR "Tai Ji"[Mesh] OR "Moxibustion"[Mesh] OR "Electroacupuncture"[Mesh] OR "Ultrasound Therapy"[Mesh] OR "Musculoskeletal Manipulations"[Mesh] OR "Electric Stimulation Therapy"[Mesh])

#6 "Treatment*" OR "Therap*" OR "Non-pharmacologic*" OR "Non-surgic*" OR "Conservativ*" OR "Rehab*" OR "Physi*" OR "Manag*"

#7 #5 OR #6

#8 (randomized OR randomised OR controlled OR double-blind OR rct)

#9 ((((("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh]) OR "Controlled Clinical Trials as Topic"[Mesh]) OR "Random Allocation"[Mesh]) OR "Double-Blind Method"[Mesh]) OR "Single-Blind Method"[Mesh]) OR ("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh])

#10 #8 OR #9

#11 "2012/01/01" [Pdat] : "2018/09/29"[Pdat]

#12 English[lang]

#13 #1 AND #4 AND #7 AND #10 AND #11 AND #12

FIGURE 1. Description of an example of online search strategy

MATERIAL AND METHODS

DATA SOURCES AND SEARCH

This systematic review was conducted following the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses) guidelines[21]. Systematic and comprehensive searches were conducted in electronic databases: MEDLINE, Embase, Physiotherapy Evidence Database (PEDro), The Cochrane Library, SciELo, Science Direct, Google Scholar, Research Gate and B-ON. Only English papers were accepted and excluded if duplicated. The search period ran from September 2018 to October 2018.

The studies selection followed the PICO model (*P*atients – Humans with knee OA; *I*ntervention – Non-surgical and non-pharmacological interventions; *C*omparison – Pharmacological, surgical, placebo, no intervention, or other non-pharmacological/non-surgical interventions; *O*utcomes – Pain, physical function and patient global assessment).

The keywords used to search in all databases were identified after preliminary literature searches and by crosschecking them against previous recent and relevant systematic reviews and umbrella reviews[22]. An example of an online search strategy draft used in MEDLINE database is presented in Figure 1.

Additional publications that were not found during the original database search were identified through manual searches in related articles and reviews reference lists.

STUDY SELECTION

In this study, two independent reviewers screened the titles and abstracts yielded by the search against the inclusion and exclusion criteria and performed the selection of the potential studies. In case of study selection disparities, the reviewers reached an agreement through verbal discussion or arbitration. Full versions for all titles that appeared to meet the inclusion criteria were achieved and then the full text versions were screened by the inclusion criteria. When insufficient data was presented, the corresponding authors were contacted by email in order to request further details. The inclusion and exclusion criteria applied to this review are described in Table I.

DATA EXTRACTION AND QUALITY ASSESSMENT

The data extracted from the selected publications to assess the effects of non-pharmacological and non-surgical interventions included[23]: authors' name, year of publication, study location, participants' sample size and their characteristics, objectives, description of the in-

TABLE I. INCLUSION AND EXCLUSION CRITERIA

Inclusion	Exclusion
The articles must include:	**The articles cannot include:**
• at least one of the keywords; • an intervention group that have primary knee OA either clinical or radiological criteria (or both); • randomized controlled trials (RCT); • non-pharmacological and non-surgical intervention; • peer-reviewed scientific literature journals; • pain, physical function and patient global assessment; • detailed description of the non-pharmacological and non-surgical intervention; • full version, in English; • studies that perform a patient global assessment using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) or Knee injury and Osteoarthritis Outcome Score (KOOS) indexes.	• an experimental or control group composed by any specie of animal; • participants that do not have a knee OA (healthy subjects) or have secondary knee OA (traumatic or post-surgical); • RCTs prior to 2012; • exclusively pharmacological or surgical interventions; • books, reviews, meta-analyses, case reports, expert opinions, conference papers or academic thesis; • subjects with other illness namely cancer, heart diseases, kidney diseases, neurological diseases, respiratory diseases, rheumatoid arthritis, gouty arthritis, septic arthritis or Paget's disease; • exclusively subjects with OA in the hip, foot, shoulder, elbow, wrist and fingers.

tervention, description of the control group, study outcomes, assessment times, study results and study conclusions. Furthermore, considering the broad scope of clinical conditions, it was decided to restrict the work to pain, physical function and patient global assessment[24].

The reviewers independently scored the methodological quality of the studies by using a validated score, the PEDro 11-items scale[25-33]. For this review only ratings of at least 6/10 on the PEDro scale were included in the analysis, consistent with previous systematic reviews[28,29,35,36]. Furthermore, principles from GRADE were used for an overall assessment and integration of the strength of the evidence for each intervention[37].

DATA SYNTHESIS AND ANALYSIS

To measure the effect magnitude of the different interventions on knee OA patients, the RevMan (Review Manager version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used to perform the meta-analysis and present the results. In relation to the meta-analysis, only studies with similar control group (sham intervention, waiting list, no intervention, daily life activities or not aware of the study), population characteristics, outcomes, instruments and follow-up, were compared in each analysis.

For the continuous outcomes, Standardized Mean Differences (SMDs) and 95% Confidence Intervals (95% CIs) were used to weigh the Effect Size (ES). The ES is used to determine the degree of improvement of a specific intervention after accounting for any placebo effect. In our study, a negative ES favored the intervention and consequently a positive ES the control. Moreover, according to Cohen's characteristics, each ES was interpreted as 0.2 (small), 0.5 (medium), and 0.8 (large)[38].

The continuous outcomes were calculated with the random-effects model using the inverse variance method. Study heterogeneity was estimated through the Higgins I^2 statistic test, subsequent x^2, and Cochran Q test, in accordance with the values of I^2 and P. Heterogeneity was interpreted by guidelines from the Cochrane Collaboration, in which, 25%, 50%, and 75% represent low, moderate and high heterogeneity, respectively[39].

RESULTS

SELECTION OF THE STUDIES

A set of 22180 records were identified through database searching. After the application of the inclusion and exclusion criteria, 52 articles have emerged. The diagram in Figure 2 summarizes the selection process.

METHODOLOGICAL QUALITY

After the selection of the studies, the reviewers inde-

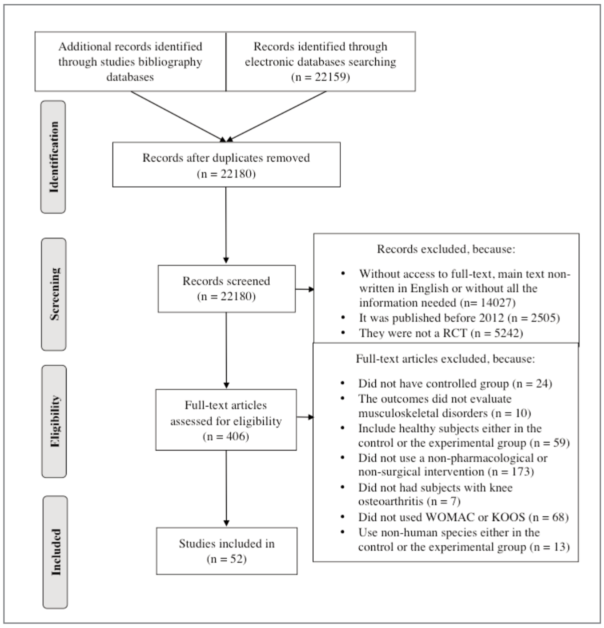

FIGURE 2. Results of the application of the inclusion and exclusion criteria.
Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score.

pendently applied the PEDro scale to evaluate the methodological quality of the 52 selected papers [40-91]. After this process, they reached an agreement through verbal discussion or arbitration. The percentage of agreement for individual items ranged from 36.36% to 100%. The methodological quality assessment using the PEDro scale revealed a mean score of 6.69 (range 3[79] – 10[91]). After the exclusion of 13 studies[42,44,46,51,53,56,63,64,73,79,80,83,90] (as they did not reach a minimum of 6/10), the mean score raised to 7.38. The classifications obtained are described in Table II.

STUDY CHARACTERISTICS

Overall, the 39 included studies[40,41,43,45,47-50,52,54,55,57-62,65-72,74-78,81,82,84-89,91] were published from 2012[41,45,58,62,66,74,81,86] to 2018[60,76,84] and conducted in America (Brazil[41,59,61,65,69,74,75,84,87] and United States of America[54,55,60,89]), Asia (China[91], India[62], Saudi Arabia[43,70], South Korea[71] and Turkey[45,47,52,66,76,77,86]), Europe (Denmark[57,67], England[78], Finland[88], Hungary[85], Italy[48,81,82] and Nederland[72]) and Oceania (Australia[49,50,58,68] and New Zealand[40]).

The total number of enrolled subjects was 3907 with an average of 99±69 (maximum=282[68], minimum=30[60]) and a mean age of 62.7±5 (maximum=74.4[82], minimum=51.9[47]) years per study. Also the follow-up period time was 20±17 (maximum=68[40], minimum=3[47,86,87]) weeks per study.

The average weight and height of all subjects were 79±8.8 (maximum=103.2[57], minimum=65[91]) kilograms and 1.63±0.06 (maximum=1.73[70], minimum=1.54[74]) meters respectively, with a mean BMI of 29.4±2.6 (maximum=37.3[57], minimum=23.9[65]) kg/m^2. More females were enrolled in the studies, specifically the number of females per study were 77±49 (maximum=179[71], minimum=0[70]), reaching a mean percentage of 72.8±18.7 (maximum=100[69,88], minimum=0[70]). Regarding the male gender the number of subjects per study were 32±32 (maximum=143[68], minimum=0[69,88]) with a percentage of 27.7±18.5 (maximum=100[70], minimum=0[69,88]).

The non-pharmacological and non-surgical treatments used in the analyzed studies were described in Figure 3.

Table III provides a summary of the study characteristics for each of the RCT's included in the review.

META-ANALYSIS

Five studies[48,61,66,68,91] meet the meta-analysis criteria. Information about different non-pharmacological and non-surgical interventions were collected, namely Acupuncture[68], Hydrotherapy[61], Interferential Current (IFC)[66], Laser[68], Moxibustion[91], Pulsed Electromagnetic Fields (PEMF)[48] and Resistance Training[60]. Due to the reduced number of studies included in the meta-analysis, only data related to Visual Analogue Scale (VAS)[48,66] and WOMAC (pain and physical function)[48,60,61,66,68,91] outcomes were collected.

VAS

Regarding the VAS outcome at week 4 (Figure 4), significant statistical differences were found ($P<0.0001$), with a mean difference of -28.47 (95% CI: -41.41, -15.53) favoring the experimental groups and a high level of heterogeneity ($Chi^2=22.25$; $I^2=87\%$) obtained. The IFC (especially at 40Hz [-36.60; 95% CI: -45.97, -27.23]) was superior to the PEMF (-11.30; 95% CI: -19.17, -3.43) intervention.

WOMAC

Regarding to WOMAC, the pain and physical function scores at week 3, 4, 6 and 12 were extracted to further analysis (Figure 5).

In WOMAC physical function, significant statistical differences between the groups (P≤0.01) at week 4, 6 and 12 were found, but not at week 3 (P=0.1), with mean differences favorable for the experimental groups (-8.89, -1.51 and -1.25 at week 4, 6 and 12 respectively). The heterogeneity was low at week 4 and 6 (I^2=24% and I^2=0%, respectively) and moderate at week 3 and 12 (I^2=26% and I^2=39%, respectively). Overall, between intervention and control it was found significant statistical differences (P<0.00001), being the experimental groups superior to control groups (-4.04; 95% CI: -6.37, -1.7), with a high heterogeneity (Chi^2=334.45; I^2=96%). Concerning the studied interventions, at week 3 and 4 IFC 100 Hz was superior (-5.9; 95% CI: -13.07, 1.27 and -9.4; 95% CI: -10.37, -8.43, respectively) to PEMF, Moxibustion, IFC 40 Hz and IFC 180 Hz; at week 6 Moxibustion was superior (-1.53; 95% CI: -2.73, -0.33) to Hydrotherapy; and at week 12 Resistance Training was superior (-3.69; 95% CI: -6.4, -0.98) to Acupuncture, Laser and Moxibustion.

The WOMAC pain outcome had a slightly different behavior compared to WOMAC physical function. Significant statistical differences between the experimental and control groups (P<0.00001) were found at week 3 and 4, with a mean difference between the groups favoring the experimental ones (-14.24 and -30.68, respectively). On other hand, at week 6 and 12 no significant statistical differences were found between the groups (P=0.06 and P=0.32, respectively), yet the mean difference between the groups favored the experimental groups (-4.68 and -3.77, respectively). The heterogeneity was high at week 3 and 12 (I^2=86% and I^2=87%, respectively) and low at week 4 and 12 (I^2=0%). Globally, the experimental group was statically (P<0.00001) superior to the control group (-14.21; 95% CI: -20.96, -7.46), however these results could be achieved by chance (Chi^2=330.67; I^2=96%). Regarding the interventions effects IFC 40 Hz was superior (-19.3; 95% CI: -22.71, -15.89) to IFC 100 Hz, IFC 180 Hz and Moxibustion at week; IFC 100 Hz was superior (-31.6; 95% CI: -35.16, -28.04) to PEMF, IFC 40 Hz and IFC 180 Hz at week 4; Moxibustion was superior (-5.27; 95% CI: -10.69, 0.15) to Hydrotherapy at week 6; and Resistance Training was superior (-14.2; 95% CI: -22.31, -6.09) to Acupuncture, Laser and Moxibustion at week 12.

DISCUSSION

In this systematic review, the interventions had different effects on the population: some improved all the outcomes evaluated; some improved only few outcomes; and others did not improve any outcome (even if the results improved comparatively to the baseline, they did not perform better than placebo interventions).

Among all the intervention studied, the results were more consistent, once again[32,33,92-96], for the positive influence of Exercise on the knee OA patients' lives. Unfortunately, due to the small number of studies gathered and different protocols used, they could not pinpoint the best type, duration, frequency or intensity of exercise that should be practiced by these patients (although Resistance Training was the one that reached the most interesting results, namely pain, strength and function[43,50,60,67]). Through analyzing the results obtained, we are lead to think that, apparently: *as long as the person does some type of exercise, he/she could benefit from it*. It has already been documented that the main positive effects of Exercise include muscular hypertrophy and strengthening, and an increase of blood flow and joint lubrication. Regarding the increase of muscular strength, whatever the neuromuscular stimulus given to someone who is not used to doing physical exercises, its short-term effects will be a rapid muscular strength increase and hypertrophy[97,98]. Therefore, since these OA patients have a more sedentary life style due to pain and functional limitations it is expected that they respond to neuromuscular stimulus in the same way as healthy people, who experience physical activity for the first time[99]. Furthermore, an increase of blood flow, joint lubrication and movement could lead to temperature, electrical and pressure changes, resulting in a decreased pain (by the gait control mechanism or the endogenous opioid system) and increased knee ROM[93,100,101]. So, the overall idea is to perform some type of physical activity that can benefit a strength increase of the thigh (with more emphasis on the quadriceps muscles) and hip muscles (important due to its biomechanical and disease relationship), adapting the volume (reps x sets x load) to the patient specificities and, at the same time, including soft cyclic movements that can be easy to learn and perform in order to increase joint lubrication. Moreover, different types of exercises should not be mixed. One explanation for the disadvantage of mixing exercises with different goals within the same session may be the molecular response, where resistance training increases the myofibrillar protein response and aerobic exercise increases the content of mitochondria in the muscle[93].

Therapeutics [E02]

- ✓ **Complementary Therapies** [E02.190]
  - Acupuncture Therapy [E02.190.044] [53, 67]
    - *Moxibustion* [E02.190.044.588] [70, 90]
  - Mind-Body Therapies [E02.190.525]
    - *Tai Ji* [E02.190.525.890] [88]
    - *Yoga* [E02.190.525.937] [54, 61]
- ✓ **Induced Hyperthermia** [E02.565]
  - Diathermy [E02.565.280] [80]
    - *Ultrasonic Therapy* [E02.565.280.945] [51, 85]
    - *Mudpack Therapy* [84]
- ✓ **Laser Therapy** [E02.594] [40, 69]
- ✓ **Magnetic Field Therapy** [E02.621] [47]
- ✓ **Nutrition Therapy** [E02.642]
  - Diet Therapy [E02.642.249] [56]
- ✓ **Rehabilitation** [E02.831]
  - Physical Therapy Modalities [E02.831.535] [48, 73]
    - *Electric Stimulation Therapy* [E02.831.535.468] [44]
      - Interferential Current [65]
      - Neuromuscular Electrical Stimulation [58, 74]
      - Transcutaneous Electric Nerve Stimulation [E02.831.535.468.800] [77]
    - *Exercise Therapy* [E02.831.535.483]
      - Focal Muscle Vibration [81]
      - Postural Balance [G11.427.690] [64, 71]
      - Resistance Training [E02.831.535.483.875] [42, 49, 59, 66]
    - *Extracorporeal Shockwave Therapy* [E02.831.535.488] [68]
    - *Hydrotherapy* [E02.831.535.492] [60, 83, 87]
    - *Musculoskeletal Manipulations* [E02.831.535.867] [39, 75]
- ✓ **Self-care** [E02.900] [57]

Equipment and Supplies [E07]

- ✓ **Bandages** [E07.101]
  - Kinesio Tape [E07.101.036] [46, 76, 86]

FIGURE 3. Non-pharmacological and non-surgical interventions used (n=39)

This molecular response will decrease when both aerobic and resistance exercises are performed within the same session[93]. The exercise choice will mainly depend on the pain, functional limitations and morphological characteristics of each patient. For instance, if a patient has a low joint limitation and a great muscular imbalance, strength exercises should be executed (greater strength and muscular growth), but if a patient has a limited knee ROM and is overweight he/she should perform low load, cyclic, aerobic exercises (greater endurance and less joint pressure)[99]. Stabilization exercises could also be added to these strength exercises, since the knee morphological changes, motivated by OA, can lead to biomechanics imbalances and, consequently, instability[4,65,72,102-104]. However, despite having interesting results, they were not better than the group that only performed strength exercises, implying that knee stability can be improved through strength training, without necessarily adding specific knee stabilization training[65,72,105,106]. Therefore, its use will depend on the degree of instability that the patient presents (if he/she has too much instability, he/she will benefit from the exercises; if diminutive instability he/she will not benefit from this type of exercises). Moreover, in some overweight patients with muscular weakness and instability, Aquatic Exercises could be a good first intervention since[61,84,88]: the possibility of having a serious injury due to fall is minimal; the joint pressure is lighten; there is weight loss; and physical performance based benefits from this type of exercise is similar from those practice on land.

In addition, these patients should preferably be supervised in their exercises as they reach better results relatively to the non-supervised ones[67]. It is important to supervise these patients not only to ensure that the exercises are correctly performed (as they are not used to doing exercises), but also to adapt the exercises to the person concerned (although we expect certain type of patient – overweight elderly woman[107] – each person will present its specific limitations), allowing the crea-

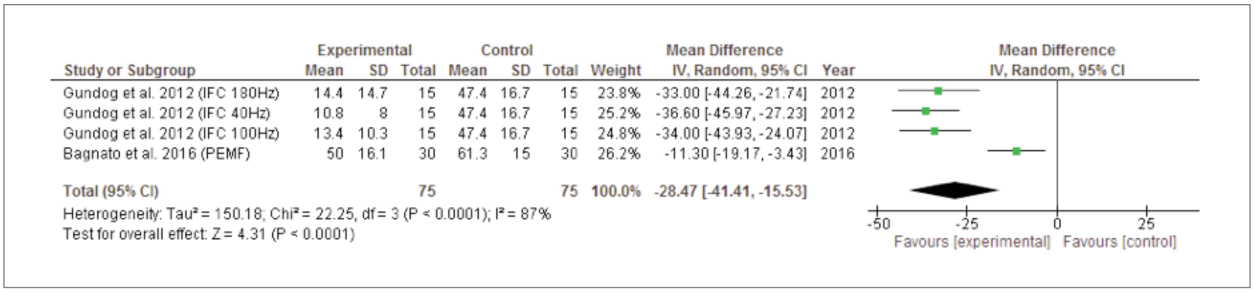

FIGURE 4. Forest plot of the effect of IFC (40, 100 and 180 Hz) and PEMF in VAS, at week 4;
The green squares indicate the effect size of each study. The transverse lines show the 95% CI of the study. Black diamond represents the pooled estimate of every subgroup and the total effect;
Abbreviations: CI, Confidence Interval; IFC, Interferential Current; IV, Inverse Variance; PEMF, Pulsed Electromagnetic Fields; SD, Standardized Errors; VAS, Visual Analog Scale.

tion of individualized goals and generating a greater impact on the patient's life[49]. Conversely, Bennell et al.[49] study did not find statistical significant differences (p>0.05) neither pain nor physical function, between those who were supervised by a physiotherapist and those who only did non-supervised home exercises. However, the authors refer that the 2 sessions over 24 weeks may have been insufficient to influence the outcomes[49]. Therefore, we recommend the use of supervision, with better results reached with those who were supervised 3 times per week. However, often these patients are not supervised with the necessary regularity, because: 1) they do not have access to a professional who helps them; or 2) with the positive evolution after treatments, they will slowly leave supervision, becoming more independent, managing in the end their issues alone. So, specific programs should be applied in order to these patients could follow in their communities and still have positive results. From the programs studied, it seems that the Osteoarthritis of the Knee Self-Management Program was the one that globally generated the greatest gains[58].

Ideally, health professionals should evaluate each patient and create individual goals. The creation of goals adapted to the patient may be important to add other interventions to Exercise. For example, if the patient is obese (a common knee OA patients characteristic) a long-term diet could be added to Exercise. It has been shown that this intervention is more powerful in the reduction of the weight kilogram (kg), weight percentage (%), BMI and fat mass after 68 weeks, in comparison to the short-term diet group plus Exercise or even those that only done Exercise[57,108]. It is also important to adapt the interventions on those who are not ready to perform exercises based on their functional limitations (an excessive muscle weakness or an extreme articular deficit) or pain (at movement or at rest). In these situations, it is necessary to perform a multimodal approach in order to improve the patients outcomes. However, due to the limited number of included studies, it is not possible to define which is the best intervention for each situation. For instance, patients that were intervened with Neuromuscular Electrical Stimulation (NMES) plus Exercise improved strength and muscular thickness over time, but were no better than those who have only done Exercise[75]. The authors explain this lack of difference by the fact that the participants had no clinically significant muscle or functional impairment and hypothesized that the greater the muscle impairment is, the greater the NMES effect will be[75]. Reflecting on this statement plus taking in consideration that those who were intervened with NMES showed better improvements in muscle thickness and anatomical cross-sectional area[59], if a patient has a major muscle deficit and is unable to perform exercise, NMES could be administrated at an early stage in an attempt to increase muscle strength; then, NMES plus some initial smooth exercises could be applied (simple, short and low load), so that the patient can have the gains associated with the exercise, in a second phase; and finally NMES can be progressively left over, focusing the time on executing strength exercises.

For an overall outcomes improvement, Moxibustion showed to be a good adjunctive intervention for knee OA patients[71,91]. The mechanisms of action of the Moxibustion Therapy remain unclear. Factors such as temperature, smoke, odor, herbs and the stimulation of acupoints are likely to be involved in the possible

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
2.1.1 WOMAC Pain, 3 weeks									
Gundog et al. 2012 (IFC 40Hz)	11.6	2	15	17.1	14	15	4.8%	-5.50 [-12.66, 1.66]	2012
Gundog et al. 2012 (IFC 100Hz)	11.2	2.2	15	17.1	14	15	4.8%	-5.90 [-13.07, 1.27]	2012
Gundog et al. 2012 (IFC 180Hz)	13.3	3.7	15	17.1	14	15	4.7%	-3.80 [-11.13, 3.53]	2012
Zhao et al. 2014 (Moxibustion)	4.8	2.47	55	5.56	3.09	55	8.6%	-0.76 [-1.81, 0.29]	2014
Subtotal (95% CI)			**100**			**100**	**22.8%**	**-2.25 [-4.91, 0.42]**	
Heterogeneity: Tau^2 = 2.53; Chi^2 = 4.07, df = 3 (P = 0.25); I^2 = 26%									
Test for overall effect: Z = 1.65 (P = 0.10)									
2.1.2 WOMAC Pain, 4 weeks									
Gundog et al. 2012 (IFC 40Hz)	7.2	1.6	15	16.1	1.5	15	8.5%	-8.90 [-10.01, -7.79]	2012
Gundog et al. 2012 (IFC 100Hz)	6.7	1.2	15	16.1	1.5	15	8.6%	-9.40 [-10.37, -8.43]	2012
Gundog et al. 2012 (IFC 180Hz)	7.8	3.3	15	16.1	1.5	15	8.3%	-8.30 [-10.13, -6.47]	2012
Bagnato et al. 2016 (PEMF)	21.6	9.6	30	26.8	8.2	30	6.6%	-5.20 [-9.72, -0.68]	2016
Subtotal (95% CI)			**75**			**75**	**31.9%**	**-8.89 [-9.73, -8.05]**	
Heterogeneity: Tau^2 = 0.18; Chi^2 = 3.95, df = 3 (P = 0.27); I^2 = 24%									
Test for overall effect: Z = 20.77 (P < 0.00001)									
2.1.3 WOMAC Pain, 6 weeks									
Zhao et al. 2014 (Moxibustion)	3.03	2.33	55	4.56	3.9	55	8.5%	-1.53 [-2.73, -0.33]	2014
Dias et. al 2017 (Hydrotherapy)	51.06	20.45	33	50.94	19.44	32	3.5%	0.12 [-9.58, 9.82]	2017
Subtotal (95% CI)			**88**			**87**	**12.0%**	**-1.51 [-2.70, -0.31]**	
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.11, df = 1 (P = 0.74); I^2 = 0%									
Test for overall effect: Z = 2.48 (P = 0.01)									
2.1.4 WOMAC Pain, 12 weeks									
Hinman et al. 2014 (Acupuncture)	6.7	3.8	64	7.3	3.9	69	8.5%	-0.60 [-1.91, 0.71]	2014
Hinman et al. 2014 (Laser)	6.6	3.9	64	7.3	3.9	69	8.5%	-0.70 [-2.03, 0.63]	2014
Zhao et al. 2014 (Moxibustion)	2.85	2.67	55	4.41	3.65	55	8.5%	-1.56 [-2.76, -0.36]	2014
DeVita et al. 2018 (Resistance Training)	3.64	2.55	15	7.33	4.72	15	7.8%	-3.69 [-6.40, -0.98]	2018
Subtotal (95% CI)			**198**			**208**	**33.3%**	**-1.25 [-2.20, -0.31]**	
Heterogeneity: Tau^2 = 0.36; Chi^2 = 4.93, df = 3 (P = 0.18); I^2 = 39%									
Test for overall effect: Z = 2.59 (P = 0.010)									
Total (95% CI)			**461**			**470**	**100.0%**	**-4.04 [-6.37, -1.70]**	
Heterogeneity: Tau^2 = 16.28; Chi^2 = 334.45, df = 13 (P < 0.00001); I^2 = 96%									
Test for overall effect: Z = 3.39 (P = 0.0007)									
Test for subgroup differences: Chi^2 = 177.17, df = 3 (P < 0.00001), I^2 = 98.3%									
2.2.1 WOMAC Physical Function, 3 weeks									
Gundog et al. 2012 (IFC 180Hz)	45.4	11.4	15	59	5.1	15	7.1%	-13.60 [-19.92, -7.28]	2012
Gundog et al. 2012 (IFC 40Hz)	39.7	4.4	15	59	5.1	15	7.5%	-19.30 [-22.71, -15.89]	2012
Gundog et al. 2012 (IFC 100Hz)	40.9	4.8	15	59	5.1	15	7.5%	-18.10 [-21.64, -14.56]	2012
Zhao et al. 2014 (Moxibustion)	22.1	14.34	55	26.71	15.6	55	7.2%	-4.61 [-10.21, 0.99]	2014
Subtotal (95% CI)			**100**			**100**	**29.3%**	**-14.24 [-20.21, -8.27]**	
Heterogeneity: Tau^2 = 31.18; Chi^2 = 21.38, df = 3 (P < 0.0001); I^2 = 86%									
Test for overall effect: Z = 4.67 (P < 0.00001)									
2.2.2 WOMAC Physical Function, 4 weeks									
Gundog et al. 2012 (IFC 40Hz)	27.2	5	15	57.8	6.1	15	7.4%	-30.60 [-34.59, -26.61]	2012
Gundog et al. 2012 (IFC 180Hz)	29.1	10.7	15	57.8	6.1	15	7.2%	-28.70 [-34.93, -22.47]	2012
Gundog et al. 2012 (IFC 100Hz)	26.2	3.5	15	57.8	6.1	15	7.5%	-31.60 [-35.16, -28.04]	2012
Bagnato et al. 2016 (PEMF)	61.7	3.79	30	89.7	34.4	30	6.1%	-28.00 [-40.38, -15.62]	2016
Subtotal (95% CI)			**75**			**75**	**28.1%**	**-30.68 [-33.07, -28.28]**	
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.83, df = 3 (P = 0.84); I^2 = 0%									
Test for overall effect: Z = 25.08 (P < 0.00001)									
2.2.3 WOMAC Physical Function, 6 weeks									
Zhao et al. 2014 (Moxibustion)	16.43	12.16	55	21.7	16.53	55	7.3%	-5.27 [-10.69, 0.15]	2014
Dias et. al 2017 (Hydrotherapy)	52.76	20.58	33	55.34	21.41	32	6.5%	-2.58 [-12.79, 7.63]	2017
Subtotal (95% CI)			**88**			**87**	**13.7%**	**-4.68 [-9.47, 0.11]**	
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.21, df = 1 (P = 0.65); I^2 = 0%									
Test for overall effect: Z = 1.91 (P = 0.06)									
2.2.4 WOMAC Physical Function, 12 weeks									
Hinman et al. 2014 (Laser)	21.9	12.3	64	23	13.2	69	7.4%	-1.10 [-5.43, 3.23]	2014
Zhao et al. 2014 (Moxibustion)	14.61	12.66	55	21.98	17.94	55	7.2%	-7.37 [-13.17, -1.57]	2014
Hinman et al. 2014 (Acupuncture)	28.5	13.1	64	23	13.2	69	7.4%	5.50 [1.03, 9.97]	2014
DeVita et al. 2018 (Resistance Training)	6.8	9.5	15	21	12.9	15	6.9%	-14.20 [-22.31, -6.09]	2018
Subtotal (95% CI)			**198**			**208**	**28.8%**	**-3.77 [-11.22, 3.69]**	
Heterogeneity: Tau^2 = 49.26; Chi^2 = 22.80, df = 3 (P < 0.0001); I^2 = 87%									
Test for overall effect: Z = 0.99 (P = 0.32)									
Total (95% CI)			**461**			**470**	**100.0%**	**-14.21 [-20.96, -7.46]**	
Heterogeneity: Tau^2 = 155.86; Chi^2 = 330.67, df = 13 (P < 0.00001); I^2 = 96%									
Test for overall effect: Z = 4.12 (P < 0.0001)									
Test for subgroup differences: Chi^2 = 129.37, df = 3 (P < 0.00001), I^2 = 97.7%									

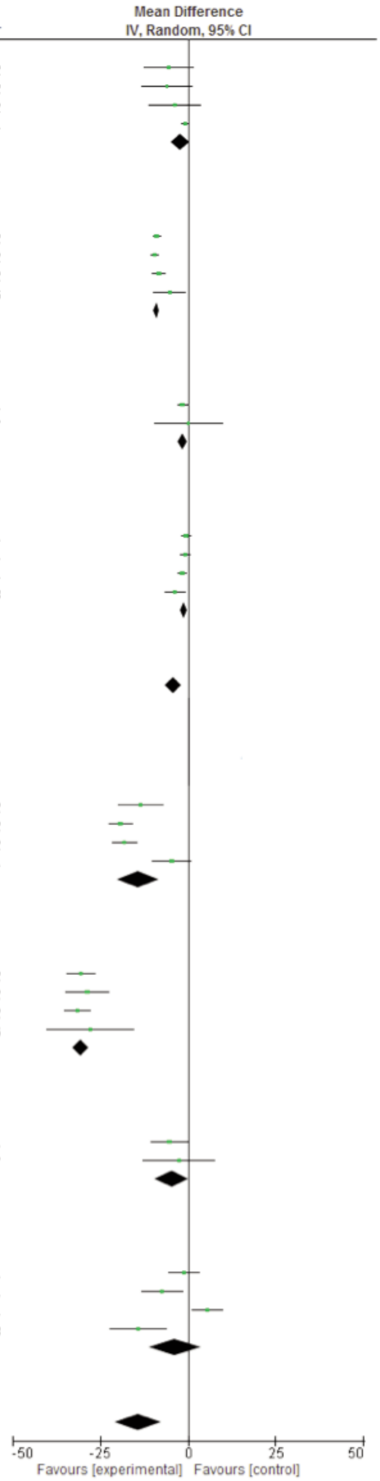

FIGURE 5. Forest plot of the effect of Acupuncture, Hydrotherapy, IFC (40, 100 and 180 Hz), Laser, Moxibustion, PEMF and Resistance Training in WOMAC physical function and pain, at week 3, 4, 6 and 12;
The green squares indicate the effect size of each study. The transverse lines show the 95% CI of the study. Black diamond represents the pooled estimate of every subgroup and the total effect;
Abbreviations: CI, Confidence Interval; IFC, Interferential Current; IV, Inverse Variance; PEMF, Pulsed Electromagnetic Fields; SD, Standardized Errors; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

mechanisms by which Moxibustion may work[91,109]. Moxibustion treatment is similar to acupuncture in principle, however the surface of the skin is only stimulated with heat at acupoints[91,109]. One of the most widely accepted mechanisms responsible for reaching positive results is the correct stimulation of acupoints, where a 2012 systematic review already confirmed that the stimulation of acupoints with needles relieves pain and improves function in knee OA patients[110]. However, in our study, acupuncture reaches mixed results, since the Hinman et al.[68] study showed significant statistical differences (P<0.05) between the needle group and the control group in the pain (short and long-term) and WOMAC (short-term) outcomes, while in the Chen et al.[54] no significant statistical differences (P>0.05) between the needle group and the sham needle group were found in all evaluated outcomes. Although the results point to a positive effect, their use cannot be fully recommended. The other Moxibustion mechanism that also creates consensus is the thermal stimulation, which might activate the sensory nervous system (thermoreceptors) through peripheral nerves such as C fibers and A delta fibers, transmitting sensory input to the central nerve system, which activates neurons to release beta endorphins and other neurotransmitters[91,109]. Meanwhile, the afferent sensory input triggers the descending inhibitory pathway to the spinal level to intercept the pain signal[91,109,111]. Also, the heat might dilatate blood vessels, increase blood circulation and degranulate local mast cells[91,109]. These may be the same mechanisms that explain the effects (pain and joint stiffness decreasing, and joint function improving) achieved by Mudpack[85] and deep heat[81] interventions. Additionally, Moxibustion is a relatively safe intervention (only skin flushing is observed, however it disappeared within 3 days), so its use can be recommended, following previous systematic reviews[109,112].

Electrotherapy interventions exhibited diverse effects. After the IFC intervention, patients improved the outcomes overtime, especially pain and function[45,66], even when compared to their placebo intervention[66]. However, compared to its placebo intervention plus Exercise, IFC did not show significant statistical differences (P>0.05)[45]. The same study[45] and the Palmer et al.[78] study also reinforced the positive impact of exercise on the patient life, as the TENS intervention obtained the same pattern as IFC, where the active TENS group, although the evaluated outcomes have improved overtime, it did not show significant statistical differences (P>0.05) comparing with sham TENS plus Exercise or even with Exercise alone. Furthermore, the Mascarin et al.[74] study also confirms that including TENS to Exercise is not more beneficial than Exercise alone, and even comparing with a group that was intervened with US plus Exercise, the TENS group was only better in the WOMAC physical function and total scores (P<0.05). This lack of positive effects using US is reinforced by the Anwer et al.[43], Ulus et al.[86] and Cakir et al.[52] studies, as active US was not better than the sham US or the control groups. Similarly, Mutlu et al.[76] compared different Musculoskeletal Manipulations (MM) (active and passive mobilization) against Electrotherapy (TENS plus US) as an adjunct interventions to Exercise and find that 12 sessions of active or passive mobilizations had a better long-term results (1 year) that just Electrotherapy, especially in knee flexion and extension (P<0.05). Abbott et al. [40] also confirms this long-term results however, of all evaluated outcomes, significant statistical differences (P<0.05) were only obtained in WOMAC comparing with the other groups (the differences between the authors may be explained by the protocols used and the physical therapists years of experience [36]). Other systematic reviews confirm the positive effects of MM in knee OA patients and propose that the neurophysiological effects through activating type II mechanoreceptors (inhibiting of type IV nociceptors, resulting in pain reduction) and the enhance of the Golgi tendon organ activity (causing muscle relaxation via reflex inhibition) are the main responsible mechanisms for reaching positive results[36,113,114].

Shock Wave Therapy[69], Focal Muscle Vibration[82] and Pulsed Electromagnetic Field Therapy (PEMF)[48], showed to be powerful interventions (P<0.05) comparing with their placebo version. However, despite these effects, it is imprudent to recommend their use based on just one RCT on each intervention. None of the studies compared its use with Exercise or as a complement therapy to Exercise, so it is necessary to develop more high-quality studies that approach these interventions. Taking into consideration other systematic reviews[28,115], from the earlier mentioned interventions, the PEMF seems to be the most promising and consistent therapy in order to improve the patient's outcomes[115]. The explanation to these positive results relays on the subsensory-threshold pulsed electric potentials that stimulate intrinsic potentials, which alter the homoeostatic balance of cartilage matrix degradation and synthesis in favor of cartilage repair[115]. This electrical stimulation increases cartilage synthesis by down regulation of interleukin-1 and up regulation of transforming growth factor beta which lead to increased aggrecan, type II collagen, and proteoglycan content in the cartilage matrix and enhanced chondrocyte proliferation[115]. Regarding the use of Laser Therapy, the studies point out the benefit of High Level Laser Therapy compared to Low Level Laser Therapy (LLLT)[70] which, as well, did not show a long-term efficacy[41,68], confirming the results of earlier systematic reviews[116,117].

Kinesio Taping (KT) obtained poor effects, with the intervention group not being significantly better (P>0.05) compared to the control group[47,87] in all evaluated outcomes (except for pain)[77]. Those poor and dispersed results were similar to those reported in an earlier systematic review [118].

Compared to the previous known umbrella review regarding the use of non-surgical and non-pharmacological interventions for knee OA patients[22], our systematic review confirms that Exercise (especially Resistance Training) is a useful intervention on these patients and reinforces the use of Moxibustion, IFC, PEMF and MM. Acupuncture, US, LLLT, Mudpack Therapy, KT and TENS achieved heterogeneous results, which may be explained by the larger number of studies and enrolled patients.

The main limitation of this systematic review was the small number of high-quality studies founded for each intervention, with different protocols.

CONCLUSION

This systematic review and meta-analysis demonstrated that Exercise had the best positive effects on knee OA patients. Besides Exercise, PEMF and Moxibustion showed to be the most promising intervention relatively to the others. Balance Training, Diet, Diathermy, Hydrotherapy, High Level Laser Therapy, IFC, Mudpack, NEMS, MM, Shock Wave Therapy, Focal Muscle Vibration, stood out, however more studies are needed to fully recommend their use. Other interventions did not show to be effective or the results obtained were heterogeneous.

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TABLE II. METHODOLOGICAL QUALITY OF ELIGIBLE STUDIES (N = 52)

Study	PEDro Scale Items											PEDro Score	GRADE
(A to Z and year)	1a	2	3	4	5	6	7	8	9	10	11	(0 – 10)	(A to D)
Alfredo et al.[41]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Atamaz et al.[45]	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	A
Bruce-Brand et al.[51]	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5	
Chang et al.[53]	Y	Y	N	Y	N	N	N	N	N	Y	Y	4	
Coleman et al.[58]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Ebnezar et al.[62]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	B
Gundog et al.[66]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6	C
Mascarin et al.[74]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6	C
Rabini et al.[81]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Ulus et al.[86]	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	7	B
Atkins et al.[46]	Y	Y	N	Y	N	N	N	Y	N	Y	N	4	
Chen et al.[54]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	8	B
Elboim-Gabyzon et al.[63]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5	
Knoop et al.[72]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Mizusaki et al.[75]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Tefner et al.[85]	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8	B
Anwer et al.[43]	N	Y	N	Y	N	N	Y	Y	N	Y	Y	6	C
Bennell et al.[49]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	B
Bennell et al.[50]	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7	B
Cakir et al.[52]	N	Y	N	Y	Y	N	Y	Y	N	Y	Y	7	B
Cheung et al.[55]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Fazaa et al.[64]	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5	
Henriksen et al.[67]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6	C
Hinman et al.[68]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	B
Kheshie et al.[70]	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y	7	B
Kim et al.[71]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	B
Laufer et al.[73]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5	
Palmer et al.[78]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Peungsuwan et al.[80]	Y	Y	N	Y	N	N	N	N	N	Y	Y	4	
Zhao et al.[91]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	A
Abbott et al.[40]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Cho et al.[56]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5	
Christensen et al.[57]	N	Y	Y	Y	N	N	N	N	Y	Y	Y	6	C
Rabini et al.[82]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	A
Bagnato et al.[48]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9	A
de Oliveira et al.[59]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	B
Wageck et al. 87	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B
Wang et al. 89	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7	B
Apparao et al. 44	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5	
Aydoğdu et al. 47	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6	C
Dias et al.[61]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	B
Imamura et al.[69]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9	A
Gomiero et al.[65]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	B
Mutlu et al. [77]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8	B

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TABLE II. CONTINUATION

Study	PEDro Scale Items											PEDro Score	GRADE
(A to Z and year)	1a	2	3	4	5	6	7	8	9	10	11	(0 – 10)	(A to D)
Waller et al.[88]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6	C
Yeğin et al.[90]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5	
Altınbilek et al.[42]	Y	Y	N	Y	N	N	Y	Y	N	N	Y	5	
DeVita et al.[60]	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6	C
Mutlu et al.[76]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	B
Parekh et al.[79]	Y	Y	N	Y	N	N	N	N	N	N	Y	3	
Rahf et al.[83]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5	
Taglietti et al.[84]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7	B
Mode	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7	B

1 – Eligibility criteria; 2 – Random allocation; 3 – Concealed allocation; 4 – Baseline comparability; 5 – Blind subjects; 6 – Blind therapists; 7 – Blind assessors; 8 – Adequate follow-up; 9 – Intention-to-treat analysis; 10 – Between-group comparisons; 11 – Point estimates and variability;
a – Item do not contribute to the total score;
Y – Yes; N – No.

TABLE III. INCLUDE RCT'S SUMMARIES (N = 39)

Interventions (Authors)	**Objectives**	**Subjects**	**Cohorts**	**Outcome Measures**	**Results**
Acupuncture					
Chen et al.[54]	• To compare the efficacy and safety of integrating a standardized true acupuncture protocol versus non-penetrating acupuncture into exercise-based physical therapy.	• n_{Total}= 214 Gender: 51.4% (110) female; 48.6% (104) male; • $n_{Non\text{-}penetrening\ acupuncture}$= 109 Age: 60.4±11.7 years BMI: 32.6 kg/m^2 Gender: 52.3% (57) female; 47.7% (52) male; • $n_{Acupuncture}$= 104 Age: 60.5±11.1 years BMI: 33.3 kg/m^2 Gender: 51% (53) female; 49% (52) male.	• Acupuncture – *Exercise* (ROM exercises + muscle strengthening + aerobic conditioning (bike and/or treadmill apparatus) – 10-20 min, 1-2 x per week, 12 total treatments + *Acupuncture* (penetrating needles placed in the knee GB 34, SP 9, ST 36, ST 35 and Xiyan, and distal points UB 60, GB 39, SP 6, and KI 3) –20 min, 1-2x per week, 12 total treatments; • Non-penetrating acupuncture – *Exercise* (ROM exercises + muscle strengthening + aerobic conditioning (bike and/or treadmill apparatus)) – 10-20 min, 1-2 x per week, 12 total treatments + *Non-penetrating Acupuncture* (same procedures and 9 points described in the acupuncture group, however without penetrating) –20 min, 1-2x per week, 12 total treatments.	• Disability – WOMAC; • Function – 6 min walk test; • Pain – BPI; • Perception of change – PGIC; • QOL – SF-36.	• Intra-group and inter-group comparisons showed no significantly differences (P>0.05) in all evaluated variables.
Hinman et al.[68]	• To determine the efficacy of laser and needle acupuncture for KOA.	• n_{Total}= 282 Gender: 49.3% (139) female; 50.7% (143) male; • n_{Needle}= 70 Age: 64.3±8.6 years Weight: 86.3±17.7 kg Height: 1.71±0.1 m BMI: 29.8±5.8 kg/m^2 Gender: 46% (32) female; 54% (38) male; • $n_{Laser\ acupuncture}$= 71 Age: 63.4±8.7 years Weight: 89.3±20.2 Kg Height: 1.71±0.1 m BMI: 30.7±6.1 kg/m^2 Gender: 39% (28) female; 61% (43) male; • $n_{Sham\ laser\ acupuncture}$= 70 Age: 63.8±7.5 years Weight: 84.7±19.3 kg Height: 1.71±0.1 m BMI: 28.8±5.4 kg/m^2 Gender: 56% (39) female; 44% (31) male; • $n_{control}$= 71 Age: 62.7±8.7 years Weight: 85.6±20.8 kg Height: 1.7±0.11 m BMI: 29.3±5.8 kg/m^2 Gender: 56% (40) female; 44% (31) male.	• Needle – *Acupuncture needle* (usual practice using a standardized set of acupuncture points, applied a max of 6 needles (0.25x40 mm) around the knee as well as distal points) – 20 min,1-2x per week, 12 weeks; • Laser acupuncture – *LLLT* (applied in the same places has the needle group (10mW and energy 0.2 J/point output)) – 20 min, 1-2x per week, 12 weeks; • Sham laser acupuncture – The same procedures has the laser acupuncture group however without the laser functioning – 20 min, 1-2x per week, 12 weeks; • Control – The control participants were unaware of the experiment.	• Disability – WOMAC; • Pain – NPRS.	• Pain: Pain was decrease significantly (P<0.05) in all groups, in comparison to the control, except for the Sham laser acupuncture group (P=0.07) at week 12. However, at 1 year it was not found any differences (P>0.05) between control and the other groups. Additionally, it was not found significant differences in between-group comparisons (P>0.05) at week 12 and 1 year; • WOMAC: From all groups, only the needle group had statistical differences in comparison to the control (P=0.04) at week 12. However, at 1 year it was not found any differences (P>0.05) between control and the other groups. Additionally, it was not found significant differences in between-group comparisons (P>0.05) at week 12 and 1 year.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
<u>Moxibustion</u> Kim et al.[71]	• To test the effect of moxibustion on the pain and function of chronic KOA patients.	• n_{Total}= 212 Gender: 84.4% (179) female; 15.6% (33) male; • $n_{Experimental}$= 102 Age: 56 years BMI: 24.8±2.6 kg/m² Gender: 83.3% (85) female; 16.7% (17) male; • $n_{Control}$= 110 Age: 57 years BMI: 24.1±2.9 kg/m² Gender: 85.5% (94) female; 14.5% (16) male.	• Experimental – *Moxibustion* (moxibustion, burning mug wort devices over 6 acupuncture points (ST36, ST35, ST34, SP9, ExLE04 and SP10) and 2 Ashi points in the affected knee) + *Educational leaflet* (containing basic information about KOA such as definition, pathology, current treatment options including drug therapy, supplements and hyaluronic acid or steroid injection and recommendations on the principles of self-exercise, good postures and rules for daily activities avoiding exaggerating symptoms) + *Stretching* (hamstring + calf) – 3x per week, during 4 weeks; • Control – *Usual care* – 4 weeks	• Depression – BDI; • Disability – WOMAC; • Function – Timed-stand test, standing-balance test and 6 min walk test; • Pain – NPRS; • QOL – SF-36.	• WOMAC: The global score showed significant differences between-groups at week 5 and 13 (P<0.01) in favor for the moxibustion group. Additionally, all subcategories of WOMAC showed significant improvement following moxibustion treatment at week 5 and 13 (P<0.01); • Pain: Moxibustion treatment improved the pain significantly compared with usual care at week 5 and 13 (P<0.01); • Function: Moxibustion significantly improved knee function for standing and sitting in a chair compared to usual care at week 5 (P=0.0486) and 13 (P=0.0006). No significant improvement was observed in the standing-balance test (P=0.52 at week 5 and P=0.26 at week 13) or six-minute walk test (P=0.51 at week 5 and P=0.68 at week 13); • BDI: There was no significant difference between-groups at week 5 (P=0.34) and 13 (P=0.64); • SF-36: The physical component summary showed significant improvement following moxibustion treatment at week 5 (P=0.0299) and 13 (P=0.0023). There was no significant difference between groups in mental component summary at week 5 (P=0.2124) and 13 (P=0.3129). Bodily pain showed significant improvement following moxibustion both at week 5 (P=0.0003) and 13 (P=0.005). Physical functioning and social functioning also showed better results at week 5 (P=0.0025 and P=0.0418 respectively), but not at 13 (P=0.1214 and P=0.4487 respectively). In the role-physical, general health, vitality, role-emotional and mental health did not show any significant differences at week 5 or 13 (P<0.05).
Zhao et al. [91]	• To compare the effectiveness and safety of moxibustion vs sham moxibustion in pain of KOA patients.	• n_{Total}= 110 Age: 65.2±7.9 years Weight: 65±6.3 kg Height: 1.62±7.98 m BMI: 24.6±5.5 kg/m² Gender: 66% (73) female; 34% (37) male; • $n_{Experimental}$= 55 Age: 65.8±7.45 years Weight: 64.1±9 kg Height: 1.63±5.28 m BMI: 24.1±1.1 kg/m² Gender: 71% (39) female; 29% (16) male; • $n_{Control}$= 55 Age: 64.6±8.4 years Weight: 66±5.2 kg Height: 1.62±1.45 m BMI: 25.2±2.4 kg/m² Gender: 62% (34) female; 38% (21) male.	• Experimental – *Moxibustion* (acupoints Dubi (ST 35), extra-point Neixiyan (EX-LE 4), and an Ashi) – 20 min, 3x per week, during 6 weeks; • Control – *Sham Moxibustion* (same procedures as the experimental group, however without active moxibustion) – 20 min, 3x per week, during 6 weeks.	• Disability – WOMAC.	The WOMAC pain scores showed greater improvement in the active treatment group than in control at week 3 (P=0.012), 6 (P<0.001), 12 (P=0.002), and 24 (P=0.002) as did WOMAC physical function scores of the experimental group at week 3 (P=0.002), 6 (P=0.015), and 12 (P<0.001) but not 24 (P=0.058).

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
Mind Body Therapies					
Tai Ji Wang et al.[89]	• To compare Tai Ji with standard physical therapy for KOA patients.	• n_{Total}= 204; Age: 60 years BMI: 33 kg/m^2 Gender: 70% (143) female; 30% (61) male; • $n_{Experimental}$= 102; • $n_{Control}$= 102.	• Experimental – *Tai Ji* (warm-up + Tai Ji principles and movements + breathing techniques + relaxation methods) – 60 min, 2x per week, during 12 weeks; • Control – *Standard Physical therapy* (manual therapy or exercise) – 30 min, 2x per week, during 6 weeks + *Home exercises* – 30 min, 4x per week, during 6 weeks.	• Depression – BDI; • Disability – WOMAC; • Function – 6 min walk test and 20 m walk test; • Medication – ASES; • QOL – SF-36.	• There were no statistical differences (P>0.05) between-groups in all time and evaluated outcomes except for the BDI overall score (P=0.012) and at week 12 (P=0.002).
Yoga Ebnezar et al.[62]	• To evaluate the efficacy of integrating Hatha Yoga therapy with therapeutic exercises for KOA patients.	• n_{Total}= 250 Gender: 69.6% (174) female; 30.4% (76) male; • n_{Yoga}= 125 Age: 59.6±8.18 years Gender: 70.4% (88) female; 29.6% (37) male; • $n_{Control}$= 125 Age: 59.4±10.66 years Gender: 68.8% (86) female; 31.2% (39) male.	• Yoga – *Hatha Yoga* (yogic sukshama vyayamas + asanas + pranayama + meditation + relaxation techniques + counseling) – 40 min per day, during 2 weeks + *Physiotherapy* (TENS + US) – 10 + 10 min per day, during 2 weeks; • Control – *Exercise* (loosening and strengthening to upper and lower limb + specific knee practices + supine rest) – 40 min per day, during 2 weeks + *Physiotherapy* (TENS + US) – 10 + 10 min per day, during 2 weeks.	• Crepitus – Palpation; • Disability – WOMAC; • Edema – Palpation; • Function – 50 m time walk; • Pain – NPRS; • ROM – Goniometer; • Tenderness – Palpation.	• Pain: There was a significant difference in pain within (P<0.001) and between the groups (P<0.001) after the intervention with higher effect size in the yoga than in the control group; • WOMAC: There was a significant difference in knee disability within (P<0.001) and between the groups (P<0.001) after the intervention with higher effect size in the yoga than in the control group; • ROM: There was a significant difference within (P<0.001) and between the groups (P<0.001) in the flexion of right and left knee joints after the intervention with higher effect size in the yoga than in the control group. • Tenderness, swelling, and crepitus: Showed a significant difference within (P<0.001) and between the groups (P<0.001) after the intervention with higher effect size in the yoga than in the control group; • Function: There was a significant reduction in time within (P<0.001) and between the groups (P<0.001) after the intervention with higher effect size in the yoga than in the control group.
Cheung et al.[55]	• To assess the feasibility and potential efficacy of a Hatha Yoga in managing osteoarthritis related symptoms in older women with KOA.	• n_{Total}= 36; Age: 72 years BMI: 29 kg/m^2; • n_{Yoga}= 18 Age: 71.9 years BMI: 29.1 kg/m^2; • $n_{Control}$= 18 Age: 71.9 years BMI: 28.8 kg/m^2.	• Yoga – *Hatha Yoga* (pranas + asanas + pranayama + meditation) – 60 min per day, 1x per week, during 8 weeks + *Home Yoga* – 30 min, 4x per week, during 8 weeks; • Control – *Wait list* (no intervention) – during 8 weeks.	• Disability – WOMAC; • Physical Performance – SPPB; • QOL – SF-12; • Sleep – PSQI; • Weight – BMI.	• WOMAC: There was only found significant differences in pain (P=0.01) and stiffness (P=0.002) comparing to the control group. No significant differences (P>0.05) were found for other outcome measures after 8 weeks in the between-group analysis. In within group analysis there was found significant differences in pain (T1 vs. T2 – P=0.04 and T1 vs T3 – P=0.01), function (T1 vs T3 – P=0.008) and total (T1 vs T2 – P=0.046 and T1 vs T3 – P=0.007). No other significant differences (P>0.05) were found within outcome measures at T1 (week 4), T2 (week 8) and T3 (week 20); • SPBB: Only repeated chair stand had between-group differences (P=0.03). No significant differences (P>0.05) were found for other outcome measures after 8 weeks in the between-group analysis. In within group analysis there was

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
					found significant differences in walk (P=0.03) and global score (P=0.007) at T1 vs T2. No other significant differences (P>0.05) were found within outcome measures at T1 (week 4), T2 (week 8) and T3 (week 20); • BMI, PSQI and SF-12: no significance differences (P>0.05) in between-groups and within analysis were found at week 8, T1 vs T2, T1 vs T2 and T2 vs T3.
Diathermy					
Rabini et al. [81]	• To compare the effects of DHT and SHT in patients with symptomatic KOA, and to determine the long-term effects of heat therapy.	• n_{Total}= 54 Gender: 83.4% (45) female; 16.6% (9) male; • n_{SHT}= 27 Age: 66.3±11.6 years BMI: 27±3.9 kg/m² Gender: 81.5% (22) female; 18.5% (5) male; • n_{DHT}= 27 Age: 64±9.8 years BMI: 27.4±4.8 kg/m² Gender: 85.2% (23) female; 14.8% (4) male.	• SHT – *Diathermy* (pad of the hyperthermia device kept warm at 38°C without switching on the microwave generator) – 30 min, 3x per week, during 4 weeks; • DHT – *Diathermy* (pad placed 2 cm above the patella, with the knee at 30° of flexion. The output power was set at 40W and the silicone pad water temperature kept at 38°C. The skin pilot temperature was set to a value aimed at achieving a 1.5°C ∅T) – 30 min, 3x per week, during 4 weeks.	• Disability – WOMAC; • Pain – VAS; • Strength – BMRC.	• WOMAC: In between group comparison the DHT group was significantly better than the SHT group in all evaluated times (at least P<0.015). Furthermore, in intra-group comparisons the scores in the SHT group did not showed statically differences between times (P>0.05), yet the DHT group showed improvements (at least P<0.003) between T0 and T1, T2, T3 and T4, but not (P>0.05) in the others evaluated times intervals; • Strength: The BMRC scores did not showed a significant group effect in comparison DHT and SHT group (P>0.05). Furthermore, in intra-group comparisons the scores in the SHT group did not showed statically differences between times (P>0.05), yet the DHT group showed improvements (at least P<0.041) between T0-T2, T0-T3, T0-T4, T1-T2, T1-T3 and T1-T4, but not (P>0.05) in the others evaluated times intervals; • Pain: In between group comparison the DHT group was significantly better than the SHT group in all evaluated times (at least P<0.016). Moreover, in intra-group comparisons the scores in the SHT group did not showed statically differences between times (P>0.05), yet the DHT group showed improvements (at least P<0.004) between T0 and T1, T2, T3 and T4, but not (P>0.05) in the others evaluated times intervals.
<u>US</u>					
Ulus et al.[86]	• To evaluate the short-term effectiveness of US therapy on pain, physical function, ambulation activity, disability and psychological status in patients with KOA.	• n_{Total}= 40; • $n_{Exprimental}$= 20 Age: 60.7±10.1 years Weight: 80.7±11.6 kg Height: 1.60±0.68 m BMI: 31.6±4.4 kg/m²; • $n_{Control}$= 20 Age: 60.3±8.8 years Weight: 78±10.7 kg Height: 1.60±0.78 m BMI: 31.1±4.7 kg/m².	• Experimental – *US* (1-MHz US head, continuous mode, with intensity of 1 W/cm2, for 10 min) + *Hot packs* (20 min) + *IFC* (10 min) + *Quadriceps Isometric Exercises* (15 min) – 5 x per week, during 3 weeks; • Control – *Sham US* (same procedure described earlier but without a functional US, for 10 min) + *Hot packs* (20 min) + *IFC* (10 min) + *Quadriceps Isometric Exercises* (15 min) – 5 x per week, during 3 weeks.	• Ambulation – 50-m walking speed; • Disability – Lequesne Index; • Functional – WOMAC; • Pain – VAS; • Psychological status – HADS.	• There was not found significant statistical differences (P>0.05) in all evaluated outcomes between-group; • On other hand, pre vs post treatment, all outcomes showed statistical differences (P<0.05) in both groups.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
Cakir et al.[52]	• To compare whether the effectiveness of continuous US was superior against pulsed US and against sham US in KOA.	• n_{Total}= 60 Gender: 78.3% (47) female; 21.7% (13) male; • $n_{Continuous\ US}$= 20 Age: 56.9±8.8 years BMI: 27.9±4.4 kg/m² • Gender: 70% (14) female; 30% (6) male; • $n_{Pulsed\ US}$= 20 Age: 58.2±9.9 years BMI: 30.9±4.0 kg/m² • Gender: 80% (16) female; 20% (4) male; • $n_{Sham\ US}$= 20 Age: 57.1±7.8 years BMI: 29.5±5.9 kg/m² Gender: 85% (17) female; 15% (3) male.	• Continuous US – *US* (5-MHz US head, continuous mode, with intensity of 1 W/cm2, for 12 min) + *Home Exercises* (Quadriceps Isometric Exercises + Muscle Strength Exercises + Stretching Exercises) – 5 x per week, during 2 weeks; • Pulsed US – *US* (5-MHz US head, 1:4 pulse, with intensity of 1 W/cm2, for 12 min) + *Home Exercises* (Quadriceps Isometric Exercises + Muscle Strength Exercises + Stretching Exercises) – 5 x per week, during 2 weeks; • Sham US – *Sham US* (same procedure described earlier but without a functional US, for 12 min) + *Home Exercises* (Quadriceps Isometric Exercises + Muscle Strength Exercises + Stretching Exercises) – 5 x per week, during 2 weeks.	• Disability – WOMAC; • Function – 20-m walking time; • Pain – VAS.	• All groups showed a statistically significant improvement in all outcomes in pre vs post treatment (P<0.05); However, there was no significant difference between-groups (P>0.05).
Mudpack Tefner et al.[85]	• To evaluate the effects of Neydharting mud-pack therapy on the clinical parameters and QOL in patients with KOA.	• n_{Total}= 53 Gender: 85% (45) female; 15% (8) male; • $n_{Exprimental}$= 27; • $n_{Control}$= 26.	• Experimental – *Neydharting hot mudpack-therapy* – 30 min each session, 5 x per week, during 2 weeks; • Control – *Hot packs* – 30 min each session, 5 x per week, during 2 weeks.	• Disability – WOMAC; • Pain – VAS; • QOL – EuroQOL-5D.	• In between-group comparison, none of the outcomes showed significant (P>0.05) statistical differences; • Within group analysis both groups showed significant statistical differences (P<0.001) in all outcomes.
Laser Alfredo et al.[41]	• Evaluate the effects of LLLT in combination with exercises on pain, functionality, ROM, muscular strength and QOL in KOA patients.	• n_{Total}= 40 Gender: 77.5% (31) female; 22.5% (9) male; • n_{LLLT}= 20 Age: 61.2±7.5 years Weight: 76.3±10.3 kg Height: 1.59±0.08 m BMI: 30.2±4.1 kg/m² Gender: 75% (15) female; 25% (5) male; • $n_{Placebo}$= 20 Age: 62.3±6.87 years Weight: 74.9±15.7 kg Height: 1.59±0.09 m BMI: 29.2±5 kg/m² Gender: 80% (16) female; 20% (4) male.	• Experimental (LLLT) – *LLLT* (5 points at the medial side of the knee and in 4 points at the lateral side, at 3 J per point – wave length of 904 nm, frequency of 700 Hz, average power of 60 mW, peak power of 20W, pulse duration 4.3 ms, 50 sec per point) – 3 x per week, during 3 weeks + *Exercises* (10 min warm-up (treadmill, ergometer bike or rowing machine) + 30 min, 2-3 sets of exercises (to increase ROM, motor learning, balance coordination and strengthening) + 5 min stretching (hamstrings, quadriceps adductors and gastrocnemius)) – 3 x per week, during 8 weeks; • Control (Placebo LLLT) – *Placebo LLLT* (same procedures as the experimental group however the laser was not functioning) – 3 x per week, during 3 weeks + *Exercises* (10 min warming-up (treadmill, ergometer bike or rowing machine) + 30 min, 2-3 sets of exercises (to increase ROM, motor learning, balance coordination and/or strengthening) + 5 min lower limb stretching) – 3 x per week, during 8 weeks.	• Disability – WOMAC; • Function –Lesquene questionnaire; • Pain – VAS; • ROM – Goniometer; • Strength – Dynamometer.	• WOMAC: Laser group showed significant improvement in intergroup analysis in pain (P=0.033), function (P=0.002) and total score (P=0.008) at T2 compared to T1 and pain (P=0.001), function (P=0.002) and total score (P=0.003) in T3 compared to T1. Laser group showed significant improvement in intragroup analysis in pain scores (P<0.05) and activity (P<0.001) between T1 and T2 and between T2 and T3 (P=0.001). No other statistically significant differences were found in the other variables in the laser group (P>0.05) neither the placebo group showed significant improvements for any of the variables (P>0.05); • Pain: Laser group showed significant improvement (P=0.001) in intragroup analysis between T1 and T2. No significant improvement in intergroup analysis (P>0.05), neither the placebo group showed any significant improvement in other variables; • Functionality: Laser group showed significant improvement (P=0.001) in intragroup analysis between T2 and T3. No significant improvement in intergroup analysis (P>0.05), neither the placebo group showed any significant

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
					improvement in other variables; • ROM: Laser group showed significant improvement (P=0.01) in intragroup analysis between T2 and T3. No significant improvement in intergroup analysis (P>0.05), neither the placebo group showed any significant improvement in other variables; • Strength: No significant improvement in intergroup and intragroup analysis in both groups (P>0.05).
Kheshie et al.[70]	• To compare the effects of LLLT and HLLT on pain relief and functional improvement in KOA patients.	• n_{Total}= 53 Age: 54.6±8.5 years Weight: 87±10.2 kg Height: 1.73±5.57 m BMI: 29.1±4.1 kg/m^2 Gender: 100% male; • n_{LLLT}= 18 Age: 56.6±7.9 years Weight: 85.2±14 kg Height: 1.73±4.92 m BMI: 28.6±5.2 kg/m^2; • n_{HILT}= 20 Age: 52.1±6.5 years Weight: 88.6±7.5 kg Height: 1.72±5.49 m BMI: 30±3.4 kg/m^2; • $n_{Placebo}$= 15 Age: 55.6±11 years Weight: 87±7.8 kg Height: 1.75±6.3 m BMI: 28.5±3.4 kg/m^2.	• LLLT – *LLLT* (wavelength of 830 nm, output power of 800 mW, average energy density of 50 J/cm^2, frequency of 1 KHz, and duty cycle of 80 %) – 32 min, 2x per week, 12 weeks + *Exercise* (10 min warm-up on a treadmill + ROM exercises (hip, knee, and ankle joints) + muscle strengthening (10 times/set, for 3x with a 2-min rest interval in the form of straight leg raising exercise) + flexibility exercises (5 min of self-stretching for the hamstring and calf muscles)); • HLLT – *HLLT* (initial phase with fast manual scanning with a total of 500 J + two successive sub phases of 710 and 810 mJ/cm^2 for a total of 500 J + in the joint line just proximal to the medial and lateral tibial condyles with 25 J, a fluency of 610 mJ/cm^2 + same as the initial phase except that scanning was slow manual scanning with a time of 14 sec for each point and a total of 250 J) – 15 min, 2x per week, 12 during weeks + *Exercise* (10 min warm-up on a treadmill + ROM exercises (hip, knee, and ankle joints) + muscle strengthening (10 times/set, for 3x with a 2-min rest interval in the form of straight leg raising exercise) + flexibility exercises (5 min of self-stretching for the hamstring and calf muscles)); • Placebo – *Placebo Laser* (equal to the others groups, however using sham laser) + *Exercise* (10 min warm-up on a treadmill + ROM exercises (hip, knee, and ankle joints) + muscle strengthening (10 times/set, for 3x with a 2-min rest interval in the form of straight leg raising exercise) + flexibility exercises (5 min of self-stretching for the hamstring and calf muscles).	• Disability – WOMAC; • Pain – VAS.	• Both treatments (HLLT and LLLT) combined with exercise were effective (P<0.05) modalities in decreasing the VAS and WOMAC scores after 6 weeks of treatment; • HLLT combined with exercises was more effective than LLLT combined with exercises, and both treatment modalities were better than exercises alone in the treatment of patients with KOA (P<0.05).
PEMF Bagnato et al.[48]	• To test the effectiveness of a wearable PEMF device in the management of pain in KOA patients.	• n_{Total}=60 Age: 67.7±10.9 years BMI: 27.4±4.3 kg/m^2 Gender: 72% (43) female; 28% (17) male; • $n_{Experimental}$= 30 Age: 68.6±11.9 years BMI: 27.7±4.6 kg/m^2 Gender: 70% (21) female; 30% (9) male; • $n_{Control}$= 30 Age: 66.9±10 years BMI: 27.1±4.1 kg/m^2 Gender: 87% (22) female; 13% (8) male.	• Experimental – *PEMF* (frequency is 27.12MHz, pulse rate of 1000Hz and a 100 s burst width with a peak burst output power of the 12 cm antenna of ~0.0098W that covers a surface area of ~103cm^2) – 12h per day, during 1 month; • Control – *Placebo PEMF* (same procedures as in the experimental group, however without a functional electromagnetic device) – 12h per day, during 1 month.	• Disability – WOMAC; • NSAID and analgesic intake – Self-reported; • Pain – VAS; • PPT – Tight pressure algometry; • QOL – SF-36.	• After 1 month, PEMF induced significant improvements (P<0.05), all evaluated outcomes, except for the SF-36 mental health (P=0.6). Also, after 1 month, PEMF induced a significant reduction (P<0.05) in VAS pain and WOMAC scores compared with placebo.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
Diet					
Christensen et al.[57]	• To compare results of obese KOA patients who, after an intensive weight loss regimen, received 1 year of either dietary support, a knee exercise program, or "no attention".	• n_{Total}=192 Age: 62.5 years Weight: 103.2 kg Gender: 81% (156) female; 9% (36) male; • n_{Diet}= 64 Age: 63±6.5 years Weight:103.6±14.8 kg Height:1.66±0.08 m BMI: 37.6±4.5 kg/m² Gender: 81% (52) female; 19% (12) male; • $n_{Exercise}$= 64 Age: 62.9±5.8 years Weight:101±14 kg Height:1.66±0.08 m BMI: 36.5±4.4 kg/m² Gender: 81% (52) female; 19% (12) male; • $n_{Control}$= 64 Age: 61.7±6.8 years Weight:105±16.1 kg Height:1.66±0.09 m BMI: 37.9±5.3 kg/m² Gender: 80% (51) female; 20% (13) male.	• Diet – *Initial diet* (8 week of low-energy diet 810 kcal/day plus 8 weeks of hypo-energy diet 1.250 kcal/day) + *Long-term diet* (participants met weekly at the dietary unit, attending sessions that lasted approximately 1 hour – 1x per week, during 52 weeks; • Exercise – *Initial diet* (8 week of low-energy diet 810 kcal/day plus 8 weeks of hypo-energy diet 1.250 kcal/day) + *Exercises* (participants underwent an exercise program consisting of a warm-up phase (10 minutes), a circuit-training phase (45 minutes), and a cool down/stretching phase (5 minutes)) – 3 x per week, during 52 weeks; • Control – *Initial diet* (8 week of low-energy diet 810 kcal/day plus 8 weeks of hypo-energy diet 1.250 kcal/day).	• Body composition – X-ray absorptiometry; • Disability – KOOS; • Function – 6 min walk test; • Pain – VAS; • QOL – SF-36. .	• The diet group showed to be more powerful in reduction the weight kg (P=0.002), weight % (P=0.001), weight loss (P=0.002), BMI (P=0.003) and fat mass (P=0.001) after 68 weeks follow up, in comparison to the other 2 groups. In the other evaluated outcomes there was not found any statistical differences (P>0.05).
PT Modalities					
Mascarin et al.[74]	• To evaluate the effects of kinesiotherapy, US and TENS in management of bilateral KOA.	• n_{Total}= 40; • $n_{Kinesiotherapy}$= 16 Age: 59.6±7.2 years Weight: 71.1±10.8 kg Height: 1.55±0.06 m; • n_{TENS}= 12 Age: 64.8±7.0 years Weight: 73.9±13.7 kg Height: 1.53±0.07 m; • n_{US}= 12 Age: 62.8±7.6 years Weight: 71.3±10.0 kg Height: 1.54±0.06 m.	• Kinesiotherapy – *Stretching* (done actively in all lower limb using static method – 3x each muscular group 30 sec) + *Isometric exercises* (strengthen adductor muscles + strengthen quadriceps muscles + strengthen hamstring muscles + strengthen abductor muscles – 30 reps each exercise 6 sec in max contraction and 3 sec rest between reps) – 20 min, 2x per week, 12 weeks; • TENS – *TENS* (100Hz frequency pulse width of 50 s, intensity set at the individual subject's sensorial threshold, modulation up to 50% of variation frequency, quadratic biphasic symmetrical pulse – by self-adhesive 5x5 cm percutaneous electrodes, during 20 min) + *Kinesiotherapy* (same process described earlier) – 40 min, 2x per week, 12 weeks; • US – *US* (continuous waves of 1 MHz frequency and 0.8 W/cm² – by a 5 cm diameter applicator, during 3 to 4 min) + *Kinesiotherapy* (same process described earlier) – 25 min, 2x per week, 12 weeks.	• Disability – WOMAC; • Function – 6 min walking test; • Pain – VAS; • ROM – Goniometer.	• Pain: In the intra-group comparisons (before vs. after) a significant decrease (at least P<0.009) was observed in the VAS in all groups for both knees except for the left knee in the US group (P=0.54). There were not found differences between groups (P>0.05); • ROM: In the intra-group comparisons, for extension, increases (at least P<0.003) were found in the Kinesiotherapy and TENS groups for both knees, but not in the US group (at least P>0.21). There were not significant differences in the flexion in all groups (P>0.05). There were not found differences between groups (P>0.05); • WOMAC: The WOMAC total scores and the score for each dimension improve significantly (at least P<0.01) in all groups in the intra-group comparisons. In between group comparisons the Kinesiotherapy and TENS group were better in Physical Function and Total Score (P<0.05) in comparison with US;

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
					• Function: In the intra-group comparisons it was found improvements in the Kinesiotherapy and US groups (P=0.003 and P=0.04 respectively), but not in the TENS group (P=0.61). There were not found differences between groups (P>0.05).
Bennell et al.[49]	• To investigate whether 2 additional physiotherapy visits improve the outcomes with continued home exercise over KOA patients.	• n_{Total}= 100 Age: 62.4±7.3 years Weight: 82.7±14.3 kg Height: 1.66±0.97 m BMI: 29.6±4.1 kg/m^2 Gender: 52% (52) female; 48% (48) male; • $n_{Experimental}$= 40 Age: 60.5±6.6 years Weight: 81.6±15.1 kg Height: 1.66±0.1 m BMI: 29.4±3.8 kg/m^2 Gender: 60% (24) female; 40% (16) male; • $n_{control}$= 38 Age: 63.7±7 years Weight: 82.2±13.8 Kg Height: 1.66±0.09 m BMI: 29.6±4.3 kg/m^2 Gender: 47% (18) female; 53% (20) male.	• Experimental – *Home exercises* (weight-bearing neuromuscular exercises + non–weight-bearing quadriceps strengthening exercises) + *2 Physiotherapy supervised sessions* (performed at 8 and 16 week) – 30 to 40 min, 4 x per week, during 24 weeks; • Control – *Home exercises* (weight-bearing neuromuscular exercises + non–weight-bearing quadriceps strengthening exercises) – 30 to 40 min, 4 x per week, during 24 weeks.	• Disability – WOMAC; • Pain – VAS.	• There was no significant difference between groups for pain or WOMAC (P>0.05).
Electric Stimulation Atamaz et al.[45]	• To compare the effectiveness of TENS, IFCs, and SWD against each other and sham intervention with exercise training and education as a multimodal package.	• n_{Total}= 203 Gender: 82.3% (167) female; 17.7% (36) male; • n_{TENS}= 37 Age: 61.9±6.9 years BMI: 28.4±3.5 kg/m^2 Gender: 83.8% (31) female; 16.2% (6) male; • $n_{TENS\ Sham}$= 37 Age: 60.7±6.5 years BMI: 29±4.1 kg/m^2 Gender: 73% (27) female; 27% (10) male; • n_{IFC}= 31 Age: 62±7.9 years BMI: 29.8±3.4 kg/m^2 Gender: 87.1% (27) female; 12.9% (4) male; • $n_{IFC\ Sham}$= 35 Age: 61.3±7.8 years	• TENS – *TENS* (80Hz frequency with 10 to 30mA intensity for 20 min – 4 surface electrodes (5x5 cm) placed over the painful area) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period + 10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks; • TENS Sham – *TENS Sham* (same procedures as TENS group however the machine was not working) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period + 10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks; • IFC – *IFC* (100Hz frequency generated by 4kHz sinusoidal waves for 20 min – 2 electrodes (8x6 cm) were placed onto the knee region) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period + 10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks; • IFC Sham – *IFC Sham* (same procedures as IFC group however the machine was not working) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period + 10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks; • SWD – *SWD* (27.12MHz frequency, an input of 300W and a mean output of 3.2W) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period +	• Disability – WOMAC and NHP; • Function – 15 m time to walk; • Pain – VAS; • ROM – Goniometer.	• A significant improvement (P<0.05) was found in VAS, WOMAC (function), NHP and 15 m time to walk in all treatment groups over time, yet without a significant difference among the groups (P>0.05); • In paired comparison (treatment vs sham) no significant differences (P>0.05) were found in all group within the variables studied.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
		BMI: 30.4±4.9 kg/m² Gender: 80% (28) female; 20% (7) male; • n_{SWD}= 31 Age: 61.6±7.4 years BMI: 28.5±4.2 kg/m² Gender: 87.1% (27) female; 12.9% (4) male; • $n_{SWD\ Sham}$= 32 Age: 61.4±8.2 years BMI: 29.3±3.4 kg/m² Gender: 84.4% (27) female; 15.6% (5) male.	10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks; • SWD Sham – *SWD Sham* (same procedures as SWD group however the machine was not working) – 5 x per week, during 3 weeks + *Exercises* (warm-up (5 to 6 min jogging period + 10 min stretching exercises) + strengthening exercises (isometric quadriceps + chair lift + minisquats) – 3 x per week, during 3 weeks.		
IFC Gundog et al.[66]	• To compare the effectiveness of different amplitude-modulated frequencies of IFC and sham IFC on KOA.	• n_{Total}=60 Gender: 80% (48) female; 20% (12) male; • $n_{IFC\ 40}$= 15 Age: 59.6±8.4 years BMI: 28.1±3.5 kg/m² Gender: 80% (12) female; 20% (3) male; • $n_{IFC\ 100}$= 15 Age: 59.6±8.1 years BMI: 29.5±4.3 kg/m² Gender: 80% (12) female; 20% (3) male; • $n_{IFC\ 180}$= 15 Age: 60.2±8.6 years BMI: 28.7±4.5 kg/m² Gender: 80% (12) female; 20% (3) male; • $n_{Sham\ IFC}$= 15 Age: 60.5±8.6 years BMI: 28.8±2.7 kg/m² Gender: 80% (12) female; 20% (3) male.	• IFC 40 – *IFC* (40Hz frequency generated by bipolar 4kHz applied by two electrodes (8x6 cm) placed laterally on the patella) – 20 min each session, 5x per week, during 3 weeks; • IFC 100 – *IFC* (100Hz frequency generated by bipolar 4kHz applied by two electrodes (8x6 cm) placed laterally on the patella) – 20 min each session, 5x per week, during 3 weeks; • IFC 180 – *IFC* (180Hz frequency generated by bipolar 4kHz applied by two electrodes (8x6 cm) placed laterally on the patella) – 20 min each session, 5x per week, during 3 weeks; • Sham IFC – (pads in the same location described earlier, but no electrical stimulation was applied to the probes) – 20 min each session, 5x per week, during 3 weeks.	• Disability – WOMAC; • Function – 15m walking time; • Pain – VAS; • ROM – Goniometer.	• All variables of all groups improved significantly (P<0.05), comparing with their baseline, immediately after treatment and at 1 moth follow-up. The only exception was in WOMAC stiffness in the IFC 180 and Sham IFC groups, after treatment and at 1 month.
NMES Mizusaki et al.[75]	• To investigate the effect NMES plus Exercise on pain and functional improvement in KOA patients compared to exercise alone.	• n_{Total}= 100 • Gender: 86% (86) female; 14% (14) male; • $n_{Experimental}$= 50 Age: 60.6±6.7 years BMI: 30.1±3.8 kg/m² Gender: 92% (46) female; 8% (4) male; • $n_{Control}$= 50 Age: 61.5±6.9 years BMI: 29.7±4.1 kg/m² Gender: 80% (40) female; 20% (10) male.	• Experimental – *NMES* (two 7.5 × 13 cm self-adhesive electrodes placed over the quadriceps) pulsed current, biphasic, asymmetrical, rectangular waveform, frequency 50Hz, pulse duration 250 s, contraction time 10 sec, rest time 30 sec every 20 min + *Exercise* (10 min on a stationary bicycle + stretching of hamstring muscles (3 reps of 30 sec) with the aid of an elastic band + loaded quadriceps strengthening exercises combined with NMES) – 2x per week, 8 weeks, 40 min each session; • Control – *Exercise* (10 min on a stationary bicycle + stretching of hamstring muscles (3 reps of 30 sec) with the aid of an elastic band + knee extension exercises performed for 3 sets of 15 reps with rest intervals of 30-45 sec between set) – 2x per week, 8 weeks, 40 min each session;	• Disability – WOMAC; • Function – TUG; • Pain – NPRS.	• Both groups improve significantly (P<0.05) in comparison with the baseline in all evaluated variables. However, there were not significant different (P>0.05) in between-group comparison in all evaluated variables.

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TABLE III. CONTINUATION

Interventions (Authors)	**Objectives**	**Subjects**	**Cohorts**	**Outcome Measures**	**Results**
de Oliveira et al.[59]	• To determine the effects of NEMS and LLLT on neuromuscular parameters and health status in KOA patients.	• n_{Total}=44; • n_{NEMS}= 15 Age: 69.3±5.5 years Height: 1.52±0.1 m Weight: 77.5±13.7 kg; • n_{LLLT}= 15 Age: 67.7±4.7 years Height: 1.59±0.1 m Weight: 74.7±11.1 kg; • $n_{Combined}$= 14 Age: 69.6±4.7 years Height: 1.55±0.15 m Weight: 70.9±8.9 kg.	• NEMS – *NEMS* (pulsed current, stimulation frequency 80 Hz, pulse duration 400 s, stimulation intensity 40% of maximal isometric voluntary contraction) – 18-32 min, 2x per week, during 8 weeks; • LLLT – *Laser* (dose 4–6 J per point, 6 points at the knee joint, 30 sec per point) – 2-3 min, 2x per week, during 8 weeks; • Combined – *NEMS* (pulsed current, stimulation frequency 80 Hz, pulse duration 400 s, stimulation intensity 40% of maximal isometric voluntary contraction) + *Laser* (dose 4–6 J per point, 6 points at the knee joint) – 20-35 min, 2x per week, during 8 weeks.	• Disability – WOMAC; • Knee extensors' electrical activity – Electromyography; • Knee extensors' strength – Dynamometry; • Muscle thickness and anatomical cross-sectional area – Ultrasonography.	• Knee extensors' electrical activity and strength: All groups had significant improvements in comparison with the baseline (P<0.05). However in between-group comparison there was not found any differences (P>0.05); • Muscle thickness and anatomical cross-sectional area: There was found significant improvements in comparison with the baseline in all groups (P<0.05) except for the LLLT group (P>0.05). Additionally, both NMES and Combined group had significant differences in comparison with the LLLT group (P<0.05); • WOMAC: All groups had significant improvements in comparison with the baseline (P<0.05).
TENS Palmer et al.[78]	• To determine the additional effects of TENS for KOA when combined with a group education and exercise program.	• n_{Total}= 224 Age: 61.4±10.5 years BMI: 29.6±8.4 kg/m² Gender: 63% (141) female; 37% (83) male; • $n_{TENS\ and\ Knee}$= 73 Age: 61.2±11.4 years BMI: 24.8±2.6 kg/m² Gender: 64.4% (47) female; 35.6% (26) male; • $n_{Sham\ TENS\ and\ Knee}$=74 Age: 60.9±10.8 years BMI: 29.1±9 kg/m² Gender: 66.2% (49) female; 33.8% (25) male; • n_{Knee}= 77 Age: 62±9.4 years BMI: 29.8±7.4 kg/m² Gender: 49.4% (38) female; 50.6% (39) male.	• TENS and Knee – *TENS* (electrical pulses asymmetric and biphasic in continuous mode at 110Hz and 50 s with 2 electrodes on the medial and other 2 on the lateral aspect on either side of the joint line) – 30 min, 6 weeks + *Exercise* (education (personal objectives + pacing + managing flares + diet + medical management of KOA + local community exercise opportunities + long-term exercise adherence) + exercises (5 min warm-up + improving lower extremity strength + proprioception + function)– 1h, 6 weeks; • Sham TENS and Knee – *TENS dummy device* (same procedures described in the active TENS) + *Exercise* (education (personal objectives + pacing + managing flares + diet + medical management of KOA + local community exercise opportunities + long-term exercise adherence) + exercises (5 min warm-up + improving lower extremity strength + proprioception + function) – 1h, 6 weeks; • Knee – *Exercise* (education) personal objectives + pacing + managing flares + diet + medical management of KOA + local community exercise opportunities + long-term exercise adherence) + exercises (5 min warm-up + improving lower extremity strength + proprioception + function) – 1h, 6 weeks.	• Adherence – 5-point Likert scale; • Change – 7-point Likert scale; • Disability – WOMAC; • Self-efficacy – 5-point Likert scale. • Strength – Digital myometer.	• All outcomes improved over time (P<0.05). However, there were no differences between trial arms and time x trial arms (P>0.05) in the outcomes.
Exercise *FMV* Rabini et al.[82]	• To evaluate the effects of FMV on physical functioning in symptomatic KOA patients.	• n_{Total}=50 Gender: 78% (39) female; 22% (11) male; • $n_{Experimental}$= 25 Age: 73.7±5.2 years Gender: 92% (22) female; 6% (3) male; • $n_{Control}$= 25 Age: 75.1±5.7 years Gender: 84% (17) female; 16% (8) male.	• Experimental – *Focal Muscles Vibration* (applied bilaterally with a fixed frequency of 100 Hz and an amplitude of approximately 0.2-0.5 mm on the distal part of the quadriceps, in the insertion of the intermedius femoris, rectus femoris, vastus femoris and vastus lateralis muscles) – 10 min, 3 applications per day, during 3 consecutive days; • Control – *Sham intervention* (the same procedure has the experimental group, however without the machine touching the skin) – 10 min, 3 applications per day, during 3 consecutive days.	• Disability – WOMAC; • Function – SPPB and POMA.	• WOMAC: There were found a statistically significant difference between the groups at 3 months (P=0.0263) and 6 months (P=0.0001). There was not found any statistical differences (P>0.05) in other evaluated times; • Function: There were found a statistically significant difference between the groups at the end of the treatment (SPPB and POMA; P=0.0172 and P=0.0029) and after 3 months (SPPB and POMA; P=0.0036 and P=0.0000). There was not found any statistical differences (P>0.05) in other evaluated times.
Balance Training Knoop et al.[72]	• To investigate whether stabilization, muscle strength and performance of daily activities	• n_{Total}= 159 Gender: 61% (97) female; 39% (62) male;	• Experimental – *Exercises* (joint stabilization + strength + daily activities performance) – 2x per week, 12 weeks with a 60 min duration + *Home exercises program* – 5 x per week, 12 weeks;	• Disability – WOMAC; • Function – TUG, PSFL, WQ35, CStQ15 and QR&S39;	• No significantly differences (P>0.05) were found in both groups in almost all evaluated variables, except in GPE were it was significantly higher (P=0.04) in the experimental group in

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
	exercises are more effective than just strength and performance of daily activities exercises in KOA patients.	• $n_{Experimental}$= 80 Age: 62.1±7.6 years BMI: 28.8±4.8 kg/m² Gender: 66% (53) female; 47% (27) male; • $n_{Control}$= 79 Age: 61.8±6.6 years BMI: 28.3±4.5 kg/m² Gender: 56% (44) female; 44% (35) male.	• Control – *Exercises* (strength + daily activities performance) – 2x per week, 12 weeks with a 60 min duration + *Home exercises program* – 5 x per week, 12 weeks.	• Instability – Self-reported; • Pain – NPRS; • Perceived effect – GPE; • Proprioception – knee joint motion detection device; • Strength – Isokinetic dynamometer.	comparison with the control.
Gomiero et al.[65]	• To compare the effectiveness of sensory-motor training vs resistance training among KOA patients.	• n_{Total}= 64; Gender: 95.3% (61) female; 4.7% (3) male; • $n_{Sensory-motor}$= 32 Age: 61.6±6.8 years Weight: 75.7±13 Kg Height: 1.57±0.08 m BMI: 24.1±3.8 kg/m² Gender: 93.8% (30) female; 6.3% (2) male; • $n_{Resistance}$= 32 Age: 61.8±6.4 years Weight: 75.5±12.7 Kg Height: 1.59±0.07 m BMI: 23.6±3.5 kg/m² Gender: 96.9% (31) female; 3.1% (1) male.	• Sensory-motor – *Warm-up* (stationary bicycle for 10 minutes) + *Exercises* (agility, coordination and balance (walking in different directions following verbal commands from the therapist + crossing steps while walking + crossing steps while walking back-wards + implementing sudden changes of direction; walking on several types of surfaces + maintaining posture during use of a balance board + using a mini-trampoline to expose individuals to potentially destabilizing loads) + stretching of the quadriceps, hamstrings and triceps surae) – 2x per week, 16 weeks; • Resistance – *Warm-up* (stationary bicycle for 10 minutes) + *Exercises* (quadriceps and hamstring strengthening using ankle weights + isometric exercises for the quadriceps + stretching of the quadriceps, hamstrings and triceps surae – 10 rep x 3 sets) – 2x per week, 16 weeks.	• Balance - Tinetti balance; • Disability – WOMAC; • Function – TUG; • Pain – VAS; • QOL – Sf-36; • Strength – Isokinetic dynamometer.	• No significantly differences (P>0.05) were found in VAS, WOMAC, TUG, strength and balance in between-group comparison. SF-36 followed the same pattern in all items except in the physical role functioning where it was obtained P=0.034; • Intra-group comparison showed significantly differences with a P≤0.001 in in VAS, WOMAC, TUG, strength and balance. SF-36 followed the same pattern in all items except in the bodily pain (P=0.06), general health perceptions (P=0.098), social role functioning (P=0.932) and mental health (P=0.006).
Resistance Training					
Anwer et al.[43]	• To investigate the effects of isometric quadriceps exercise on muscle strength, pain, and function in KOA.	• n_{Total}= 42 Gender: 69% (29) female; 31% (13) male; • $n_{Experimental}$= 21 Age: 60.6±6.72 years Weight: 65±5 Kg Height: 1.57±0.43 m BMI: 26.5±1.8 kg/m²; • $n_{control}$= 21 Age: 61.5±6.94 years Weight: 65.6±4.5 Kg Height: 1.55±0.34 m BMI: 27.1±1.3 kg/m².	• Experimental – *US* (1.5W/cm², continuous mode, during 7 min) + *Exercises* (isometric quadriceps + straight leg raising + isometric hip adduction) – 5x per week, for 5 weeks; • Control – *US* (1.5W/cm², continuous mode, during 7 min) – 5x per week, for 5 weeks.	• Disability – WOMAC; • Pain – NPRS; • Strength – Gauge device.	• In between-group comparisons, the maximum isometric quadriceps strength, the pain intensity and function in the isometric exercise group at the end of the 5th week were significantly greater than those of the control group (P<0.05). • Additionally, in intra-group (baseline vs 5th week) comparisons it was found significantly improvements (P<0.05) in all evaluated outcomes in the exercise group, but not for the control group (P>0.05).
Bennell et al.[50]	• To compare the effects of neuromuscular and quadriceps strengthening on the knee adduction moment, pain and physical function in patients with medial KOA and varus malalignment.	• n_{Total}= 100 Gender: 52% (52) female; 48% (48) male; • $n_{Experimental}$= 50 Age: 62.7±7.3 years Weight: 83.8±13.5 kg Height: 1.68±0.09 m BMI: 29.6±3.9 kg/m² Gender: 52% (26) female;	• Experimental – *Neuromuscular strengthening* (forward and backward sliding or stepping + sideways exercises + functional hip muscle strengthening + functional knee muscle strengthening + step-ups and down + balance) – 30 to 40 min, 4 x per week, during 12 weeks; • Control – *Quadriceps strengthening* (quads over a roll + knee extension in sitting + knee extension with hold at 30° knee flexion + straight leg raise + outer range knee extension) – 30 to 40 min, 4 x per week, during 12 weeks.	• Alignment – 3D gait analysis; • Disability – WOMAC; • Pain – VAS.	• There was no significant between-group difference in the change in the peak knee adduction moment, pain or WOMAC (P>0.05).

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TABLE III. CONTINUATION

Interventions (Authors)	**Objectives**	**Subjects**	**Cohorts**	**Outcome Measures**	**Results**
	48% (24) male; • $n_{control}$= 50 Age: 62.2±7.4 years Weight: 81.6±15.1 kg Height: 1.65±0.1 m BMI: 29.7±4.3 kg/m^2 Gender: 52% (26) female; 48% (24) male.				
Henriksen et al.[67]	• To investigate the effects of exercise on pressure–pain sensitivity in KOA patients.	• n_{Total}= 48 Gender: 81.2% (39) female; 18.8% (9) male; • $n_{Experimental}$= 25 Age: 65±8.9 years Weight: 82.7±13.8 kg Height: 1.69±0.08 m BMI: 28.9±4.1 kg/m^2 Gender: 88% (22) female; 12% (3) male; • $n_{control}$= 23 Age: 62.3±7.1 years Weight: 82.8±15.8 kg Height: 1.71±0.09 m BMI: 28.2±4.6 kg/m^2 Gender: 74% (17) female; 26% (6) male.	• Experimental – *Supervised exercises therapy* (10 min warm-up in a bicycle ergometer + circuit training program focusing on strength + coordination exercises of the trunk, hips, and knees) – 60 min, 3x per week, during 12 weeks; • Control – *Daily life activities* – during 12 weeks.	• Disability – KOOS; • PPT and temporal summation – Cuff pressure algometry.	• Statistical differences (P<0.05) were found from baseline for the PPT, temporal summation and KOOS pain, all in favor for the experimental group. The KOOS symptoms, daily living sports/recreation and QOL did not showed any statistical differences (P>0.05).
DeVita et al.[60]	• To assess the effect of quadriceps strengthening on quadriceps muscle force, power, and work and tibiofemoral compressive loads during walking in KOA adults.	• n_{Total}= 30 Age: 57.1±7.7 years BMI: 27.1±4 kg/m^2 Gender: 60% (18) female; 40% (12) male; • $n_{Experimental}$= 15 Age: 58.1±6.5 years Height: 1.73±0.07 m Weight: 79.4±14.8 kg BMI: 26.4±4 kg/m^2 Gender: 66.7% (10) female; 33.3% (5) male; • $n_{Control}$= 15 Age: 56.2±8.9 years Height: 1.73±0.11 m Weight: 83.8.6±18.7 kg BMI: 27.9±3.9 kg/m^2 Gender: 53.3% (8) female; 46.7% (7) male;	• Experimental – *Resistance training* (warm-up (stationary bicycle or treadmill – 5 to 10 min) + leg extension, leg press and forward lunge exercises each performed - 3 sets of 10 repetitions with loads, wherein the initial two weeks were performed at 60% 3RM, the following two weeks at 70% 3RM and the remaining 8 weeks at 85% 3RM) – 60 min, 3 x per week, during 12 weeks; • Control – *No attention*	• Disability – WOMAC; • Gait analysis (muscle forces and joint compressive forces) – infrared 3D motion analysis system in combination with reflective markers and force platform; • Strength – Isokinetic dynamometer.	• Between-group comparison showed significant statistical differences (P≤0.037) in WOMAC (pain, function and total), Isokinetic quadriceps muscle strength and some Gait variables (maximum negative quadriceps power and walking velocity). The other Gait variables did not show significant statistical differences (P>0.05).
<u>SWT</u> Imamura et al.[69]	• To assess the efficacy and safety of SWT for disabling pain due to primary KOA.	• n_{Total}= 105 Gender: 100% (105) female; • $n_{Experimental}$= 52 Age: 70±6.5 years; $n_{Control}$= 53 Age: 72.4±6.5 years.	• Experimental – *SWT* (2,000 RESWT impulses per session, positive energy flux density 0.10–0.16 mJ/mm^2 and impulses with a frequency of 8 Hz) – 1 x per week, during 3 weeks; • Control – *Placebo SWT* (same procedure as the experimental group, however without a functional device) – 1 x per week, during 3 weeks.	• Disability – WOMAC; • Pain – VAS; • PPT – Lumbar, thigh and calf pressure algometry.	• Compared with placebo treatment, SWT had a statistically significant improvement only in WOMAC scores for pain and a few of the PPT measurements (P<0.05).

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
Hydrotherapy Dias et al. [61]	• To assess the impact of hydrotherapy on pain, function, and muscle function in KOA patients.	• n_{Total}= 75 Gender: 100% (75) female; • $n_{Experimental}$= 33 Age: 70.8±5 years BMI: 30.5±4.3 kg/m² • $n_{Control}$= 32 Age: 71±5.2 years BMI: 30±5.2 kg/m².	• Experimental – *Warm-up* (walking in the water increasing velocity + lower limb stretching exercises – 5 min) + *Strengthening exercises* (closed kinetic chain exercises using floats + multidirectional walking tasks – 30 min) + *Cool-down* (light walking + breathing exercises – 5 min) – 2 x per week, during 6 weeks + *Educational program* (face to face information about the diagnosis, symptoms, prognosis, and basic care of KOA during daily activities) – 1 x per week, during 6 weeks; • Control – *Educational program* (face to face information about the diagnosis, symptoms, prognosis, and basic care of KOA during daily activities) – 1 x per week, during 6 weeks.	• Disability – WOMAC; • Strength, power, and resistance – Isokinetic dynamometer.	• Between-group comparison showed significant statistical differences (P≤0.05) at WOMAC (pain and function), Strength (extension and flexion), flexion Power and extension Resistance. However, no significant statistical differences (P>0.05) were found at extension Power and flexion Resistance.
Waller et al.[88]	• To investigate the effects of 4-months intensive aquatic resistance training on body composition and walking speed in KOA patients.	• n_{Total}= 87 Gender: 100% (87) female; • $n_{Experimental}$= 43 Age: 63.8±2.4 years Height: 1.62±0.05 m Weight: 69.6±10.3 kg BMI: 26.6±3.8 kg/m² • $n_{Control}$= 44 Age: 63.9±2.4 years Height: 1.62±0.05 m Weight: 71±11.2 kg BMI: 27.1±3.5 kg/m².	• Experimental – *Aquatic resistance training* (barefoot + small resistance fins + large resistance boots) – 1 h, 3 x per week, during 6 weeks; • Control – *Usual leisure activities.*	• Body composition – X-ray absorptiometry; • Disability – KOOS; • Strength, power, and resistance – Isokinetic dynamometer; • Walking speed – UKK 2 km walking test.	• After the 4-month intervention there was a significant decrease (P≤0.004) in BMI, fat and body mass, and increase (P=0.002) in walking speed in favor of the intervention group. In contrast, lean mass and KOOS showed no change (P>0.05).
Taglietti et al.[84]	• To compare the effectiveness of aquatic exercises with patient-education in KOA patients.	• n_{Total}= 60 Gender: 68.3% (41) female; 31.7% (19) male; • $n_{Experimental}$= 31 Age: 67.3±5.9 years BMI: 29.2±0.8 kg/m² Gender: 74.2% (23) female; 25.8% (8) male; • $n_{control}$= 29 Age: 68.7±6.7 years BMI: 30.4±0.9 kg/m² Gender: 37.9% (18) female; 62.1% (11) male.	• Experimental – *Aquatic resistance training* (Warm-up (walking + patellar mobilization + stretching the leg muscles) – 5 min + Knee and hip isometric and dynamic exercises with elastic bands (gluteus, adductors and abductors, quadriceps, hamstrings, and triceps surae) – 15 min + Aerobic exercises (stationary running or deep water-running) – 20 min + Proprioceptive exercises – 10 min + Cool down (massage + relaxation) – 10 min) – 1 h, 2 x per week, during 8 weeks; • Control – *Educational program* (guidance on the disease and its complications were included strategies for pain control (cognitive and pharmacological), physical exercise, nutrition, and weight control, medications (type, interactions, side effects, and updates), balance, proprioception, preventing falls, and how to deal with chronic pain) – 2h, 1 x per week, during 8 weeks + *Home exercises* (warm-up + self-stretching + isometric and dynamic exercises + proprioceptive and functional exercises of the lower limbs + cool down) – 3 x per week, during 8 weeks.	• Depression – YGDS; • Disability – WOMAC; • Function – TUG; • Pain – VAS; • QOL – SF-36.	• In intra-group analysis (Aquatic Resistance Training group) the outcomes that showed significant statistical differences (P<0.05) were SF-36 (physical function) and WOMAC (total and pain) between the baseline and the week 8 and at 3 months; • In between-group analysis showed significant statistical differences (P<0.05) in the WOMAC total at week 8 and at month 3, and WOMAC pain at week 8. Additionally, YGDS showed a P<0.05 at the baseline; • Other outcomes did not show significant statistical differences (P>0.05) neither in intra-group analysis nor in between-group analysis in all evaluated time period.
Musculoskeletal Manipulations Abbott et al.[40]	• To investigate the addition of manual therapy to exercise therapy for the reduction of pain and increase of physical function in people with KOA, and whether "booster sessions" compared to consecutive sessions.	• n_{Total}= 75 Gender: 61.3% (46) female; 38.7% (29) male; • n_{EX}= 19 Age: 64±10 years BMI: 29.2±6.1 kg/m² Gender: 58% (11) female; 41% (8) male; • n_{EXB}= 19 Age: 65±10 years BMI: 30.2±5.6 kg/m² Gender: 58% (11) female; 41% (8) male; • n_{EXMT}= 18 Age: 61±12 years	• Exercise consecutive sessions – *Exercise* (aerobic + strengthening + neuromuscular coordination control exercises) – 45 min, 12 sessions in the first 9 weeks • Exercise booster sessions – *Exercise* (aerobic + strengthening + neuromuscular coordination control exercises) – 45 min, 12 sessions in the first 9 weeks plus 8 consecutive sessions in the first 9 weeks, 2 booster sessions at 5 months, 1 booster session at 8 months, and 1 booster session at 11 months, also for a total of 12 sessions; • Manual therapy with exercise consecutive sessions – *Exercise* (aerobic + strengthening + neuromuscular coordination control exercises) – 45 min, 12 sessions in the first 9 weeks + *Manual Therapy* (knee flexion + anteroposterior-directed force to the tibiofemoral joint + knee extension + posteroanterior-directed force to the tibiofemoral joint + patellar gliding force + manual stretch to quadriceps, hamstrings, triceps surae muscles + soft tissue manipulation) – 30 to 45 min, 12 sessions; • Manual therapy with exercise booster sessions – *Exercise* (aerobic + strengthening + neuromuscular coordination control exercises) – 45 min, 12 sessions in the first 9 weeks plus 8 consecutive sessions in the first 9 weeks, 2 booster sessions at 5 months,	• Disability – WOMAC; • Function – TUG test, the 30 sec sit-to-stand test, and the 40-meter fast-paced walk test; • Pain – NPRS.	• In the primary outcome (WOMAC) there was found significant benefit from booster sessions (P=0.009) and manual therapy (P=0.023) over exercise therapy alone after 9 weeks that maintained at 1-year follow-up (P=0.005 and P=0.021, respectively). In Pain and function it was not found statistically significant differences (P>0.05) in between-groups comparison.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
		BMI: 27.6±4.7 kg/m^2 Gender: 67% (12) female; 33% (6) male; • n_{EXBMT}= 19 Age: 64±10.2 years BMI: 29.8±6.6 kg/m^2 Gender: 63% (12) female; 37% (7) male.	1 booster session at 8 months, and 1 booster session at 11 months, also for a total of 12 sessions + *Manual Therapy* (knee flexion + anteroposterior-directed force to the tibiofemoral joint + knee extension + posteroanterior-directed force to the tibiofemoral joint + patellar gliding force + manual stretch to quadriceps, hamstrings, triceps surae muscles + soft tissue manipulation) – 30 to 45 min, 12 sessions.		
Mutlu et al. [76]	• To compare long-term results between mobilization with movements, passive joint mobilization and electrotherapy in KOA patients.	• n_{Total}= 64; Gender: 87.5% (56) female; 12.5% (8) male; • $n_{Active\ Mobilization}$= 21 Age: 54.2±7.3 years BMI: 30.8±5 kg/m^2 Gender: 100% (21) female; • $n_{Passive\ Mobilization}$= 21 Age: 56.3±6.6 years BMI: 30.7±4.3 kg/m^2 Gender: 76.2% (16) female; 23.8% (5) male; • $n_{Electrotherapy}$= 22 Age: 57.8±6.2 years BMI: 32.6±5.7 kg/m^2 Gender: 86.4% (19) female; 13.6% (3) male;	• Mobilization with movement – *Exercise* (Aerobic (static cycle – 10 min) + Active ROM (knee in extension to full-flexion + knee in flexion to full-extension exercises – 10 reps) + Strength (quadriceps isometric contractions – 10 sec, 10 reps) + Stretching (gastrocnemius-soleus + hamstring muscle stretching exercises – 30 sec, 3 reps) – 20 min, 3x per week, during 4 weeks + *Active mobilization* (Sustained manual glide of the tibia (medial, lateral, or rotation) during active knee flexion and extension (10 reps, 3 sets)) – 30 min, 3x per week, during 4 weeks + *Home exercises* (same exercises described earlier) – 2 x per day, every day, 52 weeks; • Passive Mobilization – *Exercise* (Aerobic (static cycle – 10 min) + Active ROM (knee in extension to full-flexion + knee in flexion to full-extension exercises – 10 reps) + Strength (quadriceps isometric contractions – 10 sec, 10 reps) + Stretching (gastrocnemius-soleus + hamstring muscle stretching exercises – 30 sec, 3 reps) – 20 min, 3x per week, during 4 weeks + *Passive mobilization* (Knee distraction and dorsal glides, ventral glides and patellar glides in all directions (2–3 oscillations per sec, for 1–2 min)) – 30 min, 3x per week, during 4 weeks + *Home exercises* (same exercises described earlier) – 2 x per day, every day, 52 weeks; Electrotherapy – *Exercise* (Aerobic (static cycle – 10 min) + Active ROM (knee in extension to full-flexion + knee in flexion to full-extension exercises – 10 reps) + Strength (quadriceps isometric contractions – 10 sec, 10 reps) + Stretching (gastrocnemius-soleus + hamstring muscle stretching exercises – 30 sec, 3 reps) – 20 min, 3x per week, during 4 weeks + *TENS* (4 electrodes in continuous mode, with 110 Hz and 50 s) – 20 min, 3x per week, during 4 weeks + *US* (1-MHz frequency, 0.8 W/cm^2 power, applied at the medial and lateral knee compartments) – 5 min, 3x per week, during 4 weeks+ *Home exercises* (same exercises described earlier) – 2 x per day, every day, 52 weeks.	• Disability – WOMAC; • ROM – Goniometer; • PPT – Knee pressure algometry; • Pain – VAS; • Strength – Dynamometer; • Function – ALF.	• After 4 weeks of treatment no significant statistical differences (P>0.05) were found between the three groups in all evaluated outcomes; • In 1 year, follow-up there were found significant statistical differences (P<0.05) between Active and Passive Mobilizations vs Electrotherapy groups in all outcomes, except in the WOMAC stiffness and in the right and left hamstring strength (P>0.05).
Self-care Coleman et al.[58]	To compare the effectiveness of two self-management programs in KOA patients.	• n_{Total}= 146 Gender: 75.7% (109) female; 24.3% (37) male; • $n_{Exprimental}$= 71 Age: 65±7.9 years Gender: 80.3% (57) female; 19.7% (14) male; • $n_{Control}$= 75 Age: 65±8.7 years Gender: 69.3% (52) female; 30.7% (23) male.	• Experimental – *Self-management OAK* (holistic approach including osteoarthritis explanation and implications, self-management skills (goal-setting, problem-solving, modelling, positive thinking and improving self-efficacy), medications (types, interactions and current trends), correct use of analgesia (use, therapeutic dosing, types and side effects), pain management strategies (cognitive and pharmacologic), fitness and exercise (strength, flexibility, aerobic and balance), joint protection, nutrition and weight control, fall prevention (balance and proprioception), environmental risks, poly-pharmacy and coping negative emotions) – 2.5 h per week, during 6 weeks; • Control – *Self-management ASMP* (holistic approach including osteoarthritis general overview, self-management skills (goal-setting, problem-solving, modelling, positive thinking and improving self-efficacy), medications general overview, pain management strategies (cognitive and pharmacologic), fitness and exercise general information, joint protection, nutrition and weight control, fall prevention (balance and proprioception), environmental risks, poly-pharmacy and coping negative emotions) – 2.5 h per week, during 6 weeks.	• Disability – WOMAC; • Function – TUG; • Pain – VAS; • QOL – SF-36; • ROM – Goniometer; • Strength – Dynamometer.	• WOMAC: Pain, Physical Function and Total scores improved more significantly (P<0.05) in the OAK group than in the control group in 6-month follow-up; • QOL: There were improvements (P<0.05) from baseline to 8 weeks and 6 months in the SF-36 scales Physical Function, Role Physical, Body Pain, Vitality and Social Function in the OAK group compared with the control group. • Pain: Decreased either for the OAK and control group during the 8-week intervention phase (P<0.001); • Function: The TUG test results showed a significant improvement (P<0.05) in the OAK group compared with the control group postintervention and at 6 months; • Strength: Hamstring strength improved (P<0.05) in both right and left legs in the OAK group compared with the control group at 6 months. There was no significant difference between groups in quadriceps strength in either the left or right legs; • ROM: OAK group improved significantly (P<0.05) compared with the control group the ROM in extension in both knees and flexion of the left knee.

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TABLE III. CONTINUATION

Interventions (Authors)	Objectives	Subjects	Cohorts	Outcome Measures	Results
KT					
Wageck et al.[87]	• To analyze the effects of KT in pain, swelling, strength, function and knee-related health status in KOA patients.	• n_{Total}=76 Gender: 86.8% (66) female; 13.2% (10) male; • $n_{Experimental}$= 38 Age: 69.6±6.9 years Height: 1.61±0.09 m Weight: 77.8±15 kg BMI: 30±4.9 kg/m² Gender: 92% (35) female; 8% (3) male; • $n_{Control}$= 38 Age: 68.6±6.3 years Height: 1.6±0.08 m Weight: 79.9±10.2 kg BMI: 31.3±4.1 kg/m² z Gender: 82% (31) female; 18% (7) male.	• Experimental – *KT* (KT techniques to treat pain, strength and swelling) – 4 days with the tape; • Control – *Sham KT* (2 KT I-shaped strips without any tension, across the quadriceps muscle group) – 4 days with the tape.	• Function – LKSS; • Pain – WOMAC and Lysholm; • PPT – Knee pressure algometry; • Strength – Isokinetic dynamometer; • Swelling – Volumetry and perimetry.	• There was found no significant differences (P>0.05) between the experimental group and control group for any of the outcomes investigated at the end of the 4-day intervention period, or 15 days later.
Ayğdoğdu et al.[47]	• To compare KT along with conventional treatment to conventional treatment in KOA patients.	• n_{Total}=54; • $n_{Experimental}$= 28 Age: 52.5±9.7 years Height: 1.61±0.07 m Weight: 80.8±13.1 kg BMI: 31.2±5.1 kg/m²; • $n_{Control}$= 26 Age: 51.2±8.9 years Height: 1.6±0.08 m Weight: 80.5±14.2 kg BMI: 31.5±4.7 kg/m².	• Experimental – *Usual Treatment* (Hot-packs – 20 min + US – 5min + TENS – 20 min + Exercises (stretching hamstring and quadriceps muscles and isometric and isotonic exercises for quadriceps, hip adductors, gluteus medius and maximus, open chain and closed chain exercises – 10x each exercise, during 60 min)) + *KT* (KT Y-shaped on the quadriceps femoris with 50-70% tension, proximal to distal + KT Y-shaped on the hamstring with 50-70% tension, proximal to distal) – 5x per week, during 3 weeks; • Control – *Usual Treatment* (Hot-packs – 20 min + US – 5min + TENS – 20 min + Exercises (stretching hamstring and quadriceps muscles and isometric and isotonic exercises for quadriceps, hip adductors, gluteus medius and maximus, open chain and closed chain exercises – 60 min)) – 5x per week, during 3 weeks.	• Disability – KOOS; • Pain – VAS; • ROM – Goniometer; • Strength – Dynamometer.	• Comparing with the baseline the Usual Treatment group showed significant statistical differences (P≤0.019) in all evaluated outcomes; • Comparing with the baseline the KT group showed significant statistical differences (P≤0.026) in all evaluated outcomes, except in the hamstring strength that showed a P=0.097; • Between-group analysis showed that KT group did not perform better than Usual Treatment alone in the evaluated outcomes, since all outcomes reached a P>0.05.
Mutlu et al.[77]	• To compare the effect of KT and placebo KT in KOA patients.	• n_{Total}=39; Gender: 89.7% (35) female; 10.3% (3) male; • $n_{Experimental}$= 20 Age: 54.3±6 years BMI: 30.2±3.8 kg/m² Gender: 80% (16) female; 20% (4) male; • $n_{Control}$= 19 Age: 57.1±6.3 years BMI: 31.3±6.2 kg/m² Gender: 89.5% (17) female; 10.5% (2) male.	• Experimental – *KT* (KT Y-shaped on the quadriceps femoris with 25% tension, proximal to distal + KT Y-shaped on the hamstring with 25% tension, proximal to distal) – 3 to 4-day interval between each application, total duration from 12 to 16 days; • Control – *Sham KT* (KT applied transverse to the muscle groups of the quadriceps and hamstring) – 3 to 4-day interval between each application, total duration from 12 to 16 days.	• Disability – WOMAC; • Function – ALF; • Pain – VAS; • ROM – Goniometer; • Strength – Dynamometer.	• Short-term (week 3) between-group comparison showed that KT was significantly superior (P<0.05) to Sham KT at walking and pain at activity and night. Pain at rest, stair up and down, transfers and WOMAC did not showed significantly statistical differences (P>0.05); • Long-term (1 month) between-group comparison showed that KT was significantly superior (P<0.05) to Sham KT at walking, pain at activity and knee flexion ROM. Pain at rest and night, stair up and down, transfers, WOMAC, muscular strength, knee extension and hip ROM did not show significantly statistical differences (P>0.05).

Abbreviations: **ALF**, Aggregated Locomotor Function; **ASES**, Arthritis Self-Efficacy Scale; **ASMP**, Stanford University's Arthritis Self-Management Program; **BDI**, Beck Depression Inventory; **BMRC**, British Medical Research Council; **BPI**, Brief Pain Inventory; **cm**, centimeter; **CSHQ15**, Climbing Stairs Questionnaire; **DHT**, Deep Heating Therapy; **FMV**, Focal Muscle Vibration; **GPE**, Global Perceived Effect; **h**, hour; **HADS**, Hospital Anxiety and Depression Scale; **HLLT**, High-Level Laser Therapy; **Hz**, Hertz; **IFC**, Interferential Current; **J**, Joule; **Kg**, Kilogram; **kHz**, Kilohertz; **KOA**, Knee Osteoarthritis; **KOOS**, Knee Injury and Osteoarthritis Outcome Score; **KT**, Kinesio Tape®; **LKSS**, Lysholm Knee Scoring Scale; **LLLT**, Low-Level Laser Therapy; **m**, Meter; **mA**, Milliamp; **MHz**, Megahertz; **min**, Minutes; **mJ**, Millijoule; **mm**, Millimeter; **ms**, Millisecond; **mW**, Milliwatts; **NHP**, Nottingham Health Profile; **nm**, Nanometer; **NEMS**, Neuromuscular Electrical Stimulation; **NPRS**, Numeric Pain Rating Scale; **NSAID**, Non-steroid Anti-inflammatory Drug; **OAK**, Osteoarthritis of the Knee Self-Management Program; **P**, Significance level; **PEMF**, Pulsed Electromagnetic Fields; **PGIG**, Patient Global Impression of Change; **POMA**, Performance-Oriented Mobility Assessment; **PPT**, Pressure Pain Threshold; **PSQI**, Pittsburgh Sleep Quality Index; **PSFL**, Patient Specific Functioning List; **PT**, Physical Therapy; **QOL**, Quality of Life; **QR&S39**, Questionnaire Raising and Sitting Down; **ROM**, Range of Motion; **sec**, Second; **SF-36**, Short Form 36 Health Survey; **SHT**, Superficial Heating Therapy; **SPPB**, Short Physical Performance Battery; **SWD**, Shortwave Diathermy; **SWT**, Shock Wave Therapy; **TENS**, Transcutaneous Electrical Nerve Stimulation; **TUG**, Timed Up and Go; **US**, Ultrasound; **VAS**, Visual Analog Scale; **W**, Watts; **WOMAC**, Western Ontario and McMaster Universities Osteoarthritis Index; **WQ35**, Walking Questionnaire; **YGDS**, Yesavage Geriatric Depression Scale; **μs**, Microsecond.