SICOT

(International Society of Orthopaedic Surgery and Traumatology)

Current Concepts in the Management of Osteoarthritis

Module 2

Updates on Management of Osteoarthritis and Osteoarthritis Pain

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Contents

SYLLABUS

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

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 (Patients – Humans with knee OA; Intervention – Non-surgical and nonpharmacological interventions; Comparison – Pharmacological,surgical, placebo, no intervention, or other non-pharmacological/non-surgical interventions; Outcomes – 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 world-wide suffering from this disease[8].Yet, in now a days 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 community 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-analysisis 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.

Material and methods

Data sources and search

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 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 (Patients – Humans with knee OA; Intervention – Nonsurgical and non-pharmacological interventions; Comparison– Pharmacological, surgical, placebo, no intervention, or other non-pharmacological/ non-surgical interventions;Outcomes – 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.

Key points

- 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. There are at least 151,4 million persons worldwide suffering from this disease. Yet, in nowadays these values are for sure higher, since the incidence of new cases is 200–250/100 000/year.

#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

Key points

- 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.

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 intervention, 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].

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.

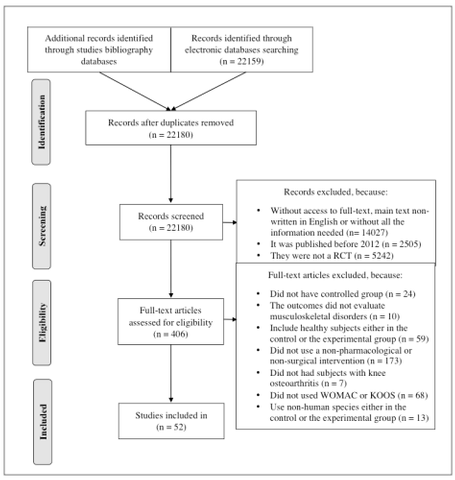

FIGURE 2. Results of the application of the inclusion and exclusion criteria.
Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee injury and Osteoarthritis Outcome Score.

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 independently 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 379 – 1091). 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 Ta-ble II.

Study characteristics

Overall, the 39 included studies4[0,41,43,45,47-50,52,54,55,57-62,65--72,74-78,81,82,84-89,91]were published from [201241,45,58,62,66,74,81,86] 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 (China91, India62, Saudi Arabia[43,70], South Korea71 and Turkey[45,47,52,66,76,77,86]), Europe (Denmark[57,67], England78, Finland[88,] Hungary85, 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=6591) kilograms and 1.63±0.06 (maximum=1.7370, minimum= 1.54[74]) meters respectively, with a mean BMI of 29.4±2.6 (maximum=37.3[57], minimum=23.9[65]) kg/m2. More females were enrolled in the studies, specifically the number of females per study were

Key points

- 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. Current OA rehabilitation strategy is a complex process that uses surgical and non-surgical interventions (pharmacological and non-pharmacological).

Key points

- The studies selection followed the PICO Model:

  Patients – Humans with knee OA

  Intervention – Nonsurgical and non-pharmacological interventions

  Comparison– Pharmacological, surgical, placebo, no intervention, or other non-pharmacological/ non- surgical interventions

  Outcomes – Pain, physical function and patient global assessment

77±49 (maximum= 17971, minimum=070), reaching a mean percentage of 72.8±18.7 (maximum=10069,88, minimum= 070). Regarding the male gender the number of subjects per study were 32±32 (maxi-mum=14368, minimum=069,88) with a percentage of 27.7±18.5 (maximum= 10070, minimum=0[69,88]).

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 (Chi2=22.25; I2=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 (I2=24% and I2=0%, respectively) and moderate at week 3 and 12 (I2=26% and I2=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 (Chi2=334.45; I2=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 (I2=86% and I2=87%, respectively) and low at week 4 and 12 (I2=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 (Chi2=330.67; I2=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 again3[2,33,92-96], 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 time99. 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 differentn 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].

This molecular response will decrease when both aerobic and resistance exercises are performed within the same session93. 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 creation 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 outcomes49. Therefore, we recommend the use of supervision, with better results reached with those who were supervised 3 times per week. However,

Key points

- The data extracted from the selected publications to assess the effects of non-pharmacological and non-surgical interventions included:
  - -Authors' name
  - -Year of publication
  - -Study location
  - -Participants' sample size and their characteristics
  - -Objectives
  - -Description of the intervention
  - -Description of the control group
  - -Study outcomes
  - -Assessment times
  - -Study results
  - - Study conclusions

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

Key points

- 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.

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

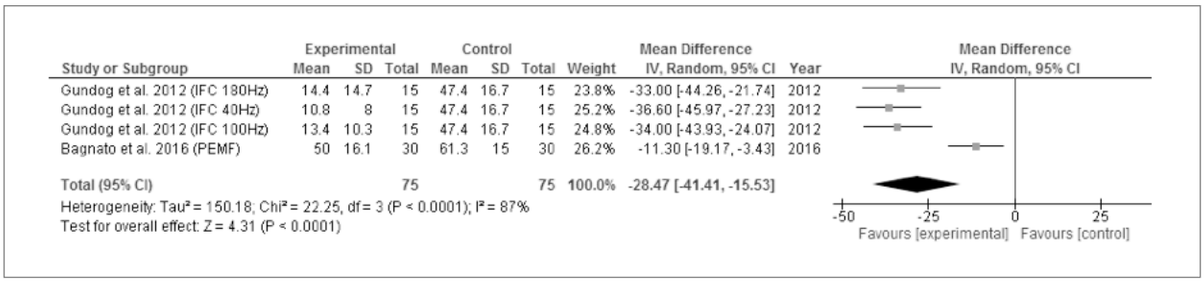

FIGURE 4. Forest plot of the effect of IFC (40, 100 and 180 Hz) and PEMF in VAS, at week 4;
The green squares indicate the effect size of each study. The transverse lines show the 95% CI of the study. Black diamond represents the pooled estimate of every subgroup and the total effect;
Abbreviations: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

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 patienthas 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 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 theresults 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 signif-

Key points

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

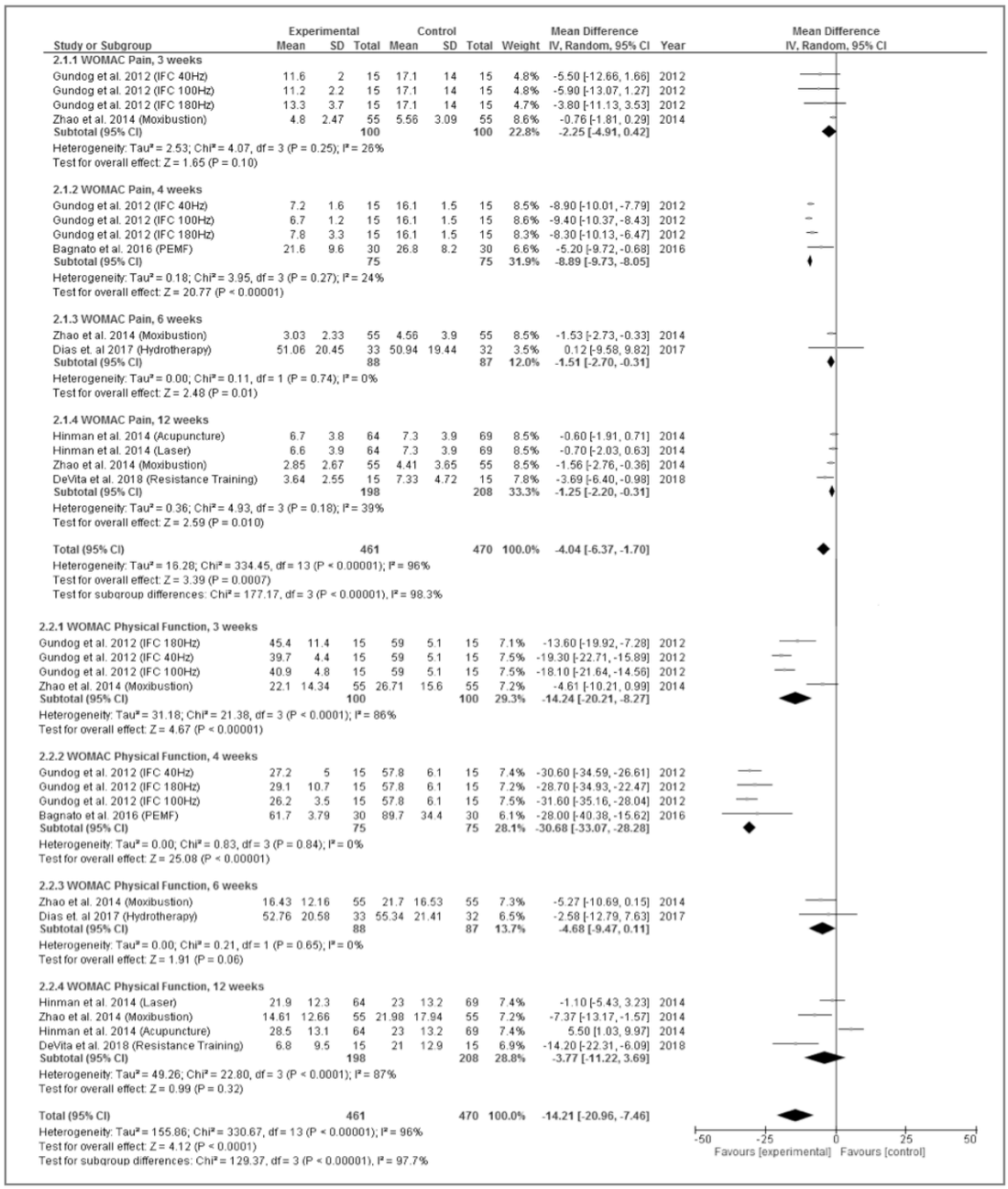

FIGURE 5.Forest plot of the effect of Acupuncture, Hydrotherapy, IFC (40, 100 and 180 Hz), Laser, Moxibustion, PEMF and Resistance Training in WOMAC physical function and pain, at week 3, 4, 6 and 12;
The green squares indicate the effect size of each study. The transverse lines show the 95% CI of the 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.

icant statistical differences (P>0.05)45. The same study45 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 thatincluding 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. HHowever, 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.

Key points

- The authors refer that the 2 sessions over 24 weeks may have been insufficient to influence the outcomes. 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
  (2) With the positive evolution after treatments, they will slowly leave Supervision, becoming more independent, managing in the end their issues alone.

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Pharmacological Treatment of Pain in Osteoarthritis: A Descriptive Review

ABSTRACT :

Purpose of Review: Osteoarthritis (OA) is the most common form of arthritis that is characterized by loss of articular cartilage and new formation of bone. Pain and functional disability are common features that lead to disability and poor quality of life. This review discusses the current state of knowledge concerning the treatment of pain in OA, with a focus on pharmacological treatments. This includes the use of non-steroidal anti-inflammatory drugs, acetaminophen, and other disease-modifying agents.

Recent Findings: An updated review of the role of anti-nerve growth factor monoclonal antibodies and other novel agents in the treatment of OA is also presented. In addition, a discussion of current research on biological agents such as small molecules targeting ion channels and G protein-coupled receptors is included. These new pharmacological interventions expand the frontier for treatment of patients with OA.

Summary: The purpose of the review is to provide clinicians with information about the effectiveness of different pharmacological modalities in order to enable them to make the best choices for the treatment of their patients.

Keywords: Osteoarthritis .Joint pain . Pharmacology . Monoclonal antibodies . NSAIDs . Acetaminophen

INTRODUCTION

Osteoarthritis (OA) is a progressive, degenerative illness of the moveable joints and typically presents with symptoms of arthralgia and functional disability [1]. Common characteristics of the illness are joint pain, progressive degeneration of the cartilage, remodeling of joint tissues, and narrowing of the joint space [2, 3]. Joints with OA show features of both inflammatory and degenerative disease that lead to pain, loss of function, disability, and poor quality of life [4]. By age 65, more than 80% of the population shows radiological evidence of the disease [5].

According to the Global Burden of Disease, more than 237 million people in the world live with OA of the hip and/or knee [6]. A decade ago, Lawrence et al. estimated that the prevalence of OA in the United States approached 27 million people [7]. It is estimated that 12–13.4% of the U.S. adult population suffers from it, making it the second most costly health condition treated in U.S. hospitals and accounting for 4.3% of combined hospital costs [8, 9]. The annual financial burden due to the morbidity of the disease is estimated to be over $16.5 bill on in hospital costs [9]

Pain experience in OA is both peripheral and central in nature. Pain originates from nociceptive, inflammatory pathways and pain is exaggerated by central sensitization [10,11]. Nocicepters in joints are stimulated by local inflammation, bone marrow lesions, neovascularization, structural bone changes such as remodeling, and the new nerve generation in cartilage, menisci, and osteophyte formation [10•]. The inflammatory process includes synovitis and effusion that precedes the structural lesions of the joints [4]. Increased production and upregulation of nerve growth factor (NGF), tumor necrosis factor alpha(TNF-alpha), and C-re-active protein in the synovium of an affected joint may lead to increased pain perception, as well [4, 12, 13•].

In the Central Nervous System (CNS), chronic cases of OA stimulate central sensitization of pain resulting in increased glutamate sensitivity and the formation of dysfunctional synaptic connections and transmission [11]. Moreover, along with hyperexcitability, CNS patients with OA experience magnified spatial summation and, as a result, also a higher insensitivity to pain [14]. Chronic arthritic pain may eventually involve the limbic system—a region involved in fear, emotions, and reward [15]. Peripheral and central sensitization of pain with dysfunction of the ascending and descending pain signals along with psychosocial factors further enhance the experience of pain in OA [10].

The primary goals in the treatment of OA are relief from pain, maximization of functioning, and slowing or halting the process of joint damage [13•]. There is currently no disease-modifying OA treatment approved by the United States Food and Drug Administration (FDA). Many non-pharmacologic and pharmacologic therapeutic modalities for the management of pain and improvement of function are currently in use, and other novel agents are being explored and developed. Due to the modest effects of the individual treatment options, a combination of therapeutic approaches is commonly used in practice [16].

Literature Survey

Studies evaluating the effect of pain medications on OA were identified through an electronic search using Google Scholar, Medline/PubMed, and the Cochrane Database of Systematic Reviews. Key search words included "osteoarthritis," "pain management," "pain," "pain medications," "pain pharmacology," "pain treatment," and "pain medicine." Studies that showed

Key points

- Osteoarthritis (OA) is a progressive, degenerative illness of the moveable joints and typically presents with symptoms of arthralgia and functional disability. Common characteristics of the illness are-
  - -Joint pain
  - -Progressive degeneration of the cartilage
  - -Remodeling of joint tissues
  - -Narrowing of the joint space

evidence of the use of medications in the treatment of pain in OA were selected.

Non-Pharmacological Measures

Non-pharmacologic interventions are the first-line therapeutic modalities and should be considered before exploring pharmacological and surgical approaches [17•]. Obesity is one of the strongest modifiable risk factors for OA and weight reduction can play an important role in management of the illness [18]. Aerobic exercises, strength training, low impact aquatic exercise, and Tai-chi are beneficial for lessening pain and increasing flexibility and function in people with OA, regardless of the severity of the disease [17•, 19]. A combination of exercise and weight reduction has been associated with a significant reduction in the morbidity caused by knee OA in overweight and obese patients [20, 21]. Cognitive behavioral therapy and mindfulness-based therapy also decrease pain perception, increase physical functioning, and reduce disability when utilized in conjunction with other therapies [22–24]

Pharmacotherapy for Osteoarthritis

Pharmacological therapy is used in patients who fail to respond to non-pharmacologic interventions to reduce pain and maximize functioning. This paper provides a summary of the current literature available on the various treatment modalities within each class of medication.

Traditional Medications

Traditional analgesics have been used for the past several decades for the treatment of pain in OA. We have briefly reviewed these medications in Table 1.

Non-Steroidal Anti-Inflammatory Drugs

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are frequently used in the treatment of OA. A few of them are available over-the-counter. The mechanisms of action of NSAIDs include both peripheral and central effects to treat pain. Peripherally, NSAIDs inhibit the activity of cyclooxygenase (COX) enzymes 1 and 2, leading to decreased synthesis prostaglandins and resulting in analgesia [33]. NSAIDs also have the additional effect of increasing serotonin in the central nervous system [34].

Topical NSAIDs and oral NSAIDs are equally effective in the treatment of localized OA [35]. Thus, use of topical NSAIDs for pain relief in OA affecting a single joint or a small number of joints is appropriate and limits the risk of side effects, as was illustrated by Kiensler et al. with topical diclofenac [36]. When diclofenac, the most commonly used topical NSAID, is applied to the skin, systemic exposure is 5 to 17 times lower than when taken orally [36]. However, even with lower blood levels, it demonstrated the same efficacy for the treatment of pain with a better systemic side effect profile than did oral preparations [36]. A randomized controlled trial showed that topical treatment with a diclofenac solution is equivalent in efficacy to oral NSAIDs in pain alleviation for knee and hand OA [26].

A meta-analysis by Bjordal et al. supported a small effect size (ES) of NSAIDs for pain reduction of 0.23 (0.15 to 0.31)

in knee OA during short-term (2–13 weeks) use [25]. However, the authors did not support chronic use in knee OA due to long-term adverse effects [25]. In another meta-analysis, NSAIDs showed small-to-moderate effectiveness ES 0.29 (0.22–0.35) in the treatment of pain in OA [28]. In a review of 273 studies of NSAID use in OA, Chou et al. noted no difference in the efficacy of different NSAIDs in pain control for OA [35]

In patients having OA involving multiple joints, or those failing to respond to topical NSAIDs, oral NSAIDs can be used for symptomatic relief. In a recent meta-analysis, six different pharmacological interventions (diclofenac 150 mg/ day, etoricoxib 30 mg/day, 60 mg/day, and 90 mg/day, and rofecoxib 25 mg/day and 50 mg/day) were evaluated. Diclofenac 150 mg/day (ES – 0.57, 95% credibility interval – 0.69 to – 0.45) and etoricoxib 60 mg/day (ES – 0.58, – 0.74 to – 0.43) provided the best pharmacological interventions available for knee and hip OA [27].

Although studies have produced many different results, NSAIDs consistently show increased risk of gastrointestinal complications by three to fivefold [37]. Even in patients without known cardiovascular diseases, most non-selective NSAIDs are associated with the increased risk of adverse cardiovascular events, including myocardial infarction, stroke, heart failure, and atrial fibrillation [38, 39]. When selected for use, NSAIDs should be prescribed at the lowest effective dose and for the shortest duration required in order to limit adverse events.

Table 1 Traditional pain medications

Medication	Reference, year	Objective	Subjects/participant	Design	Intervention	Control	Outcome
NSAIDs	Bjordal et al., 2004 [25]	Efficacy of NSAIDs in patients with OA of the knee	N = 10,845 adults, median age 62.5 years	Meta-analysis of RCT	Change in pain intensity between the NSAIDs group and placebo on VAS	Placebo	Difference on VAS was 10.1 mm (95% confidence interval 7.4 to 12.8), 15.6% better than placebo
	Derry et al., 2012 [26]	Evidence of topically applied NSAIDs for chronic musculoskeletal pain	N = 10,631 with chronic musculoskeletal pain	Meta-analysis of RCT	Participants achieving a 50% reduction in pain to calculate RR and NNT or NNH	Placebo	Participants having successful treatment with a topical diclofenac was 48% (90/189, range 44 to 52%) compared to placebo rate of 28% (53/186, range 25 to 33%)
Acetaminophen	Bruno et al., 2017 [27]	Efficacy of NSAIDs	N = 58,451 with chronic OA	Meta-analysis of RCT	RCT comparing NSAIDs, acetaminophen, or placebo, for the treatment of OA	Placebo or acetaminophen	Diclofenac 150 mg/day had maximum effect size in pain reduction (ES −0.57, 95%, CrI −0.69 to −0.45)
	Zhang et al., 2004 [28]	Efficacy of acetaminophen in the treatment of OA	N = 1712 patients with OA of the knee (6 trials) or hip/knee (3 trials) or multiple joints (1 trial)	Systematic review and meta-analysis of RCTs	ES for pain, stiffness, and functional scores	Placebo or NSAIDs	Acetaminophen with effect size (ES = 0.21, 95% CI (0.02 to 0.41) compared to NSAIDs (ES = 0.20, 95% CI 0.10 to 0.30)
Duloxetine	Raya S. et al., 2012 [29]	Efficacy of duloxetine in reducing pain in knee OA	N = 288 patients aged >/= 65 years with primary knee OA	RCT	The pain was assessed using the VAS and the WOMAC pain subscale	Placebo	WOMAC pain score (0-20); At baseline = 9.1 (4.6) At 16 weeks = 6.0 (4.1) P value = 0.05
	Frakes et al., 2011 [30]	Efficacy, and safety of duloxetine when added to oral NSAIDs in OA of the knee	N = 524 Mean age was 61 years (SD 9.)	RCT (duloxetine 60/120 mg/day)	Patients received duloxetine or placebo for 10 weeks	Placebo	Significant pain reduction and WOMAC score at week 8 with duloxetine. (P < 0.001)
	Citrome et al., 2012 [31]	Efficacy and safety of duloxetine for OA pain	N/A	Systematic review of all published double-blind RCTs of duloxetine for OA pain	NNT for pain relief NNH for relevant dichotomous adverse outcomes were extracted	Placebo	≥ 30% or ≥ 50% reduction in pain scores ranged from 42 to 67% for duloxetine, compared with 26 to 50% for placebo
Capsaicin	Mason et al., 2004 [32]	Efficacy and safety of topically applied capsaicin for chronic pain	N = 656 patients with chronic musculoskeletal pain	Randomized active or placebo-controlled trials	NNT to treat for six RCT for treatment of neuropathic conditions	Placebo or another treatment for chronic pain	NNT was 6.4 (95% CI, 3.8 to 21). The mean response at 8 weeks for capsaicin 0.075% was 60% (range 20 to 75%)

CI,confidence interval;CrI,credibility index; ES,effectsize; NNH, number neededtoharm; NNT, numberneededottreat; RCT,randomized controlled clinical trial;RR, risk ratio;VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Key points

- Joints with OA show features of both inflammatory and degenerative disease that lead to-
  - -Pain
  - -Loss of function
  - -Disability
  - -Poor quality of life
- By age 65, more than 80% of the population shows radiological evidence of the disease. According to the Global Burden of Disease, more than 237 million people in the world live with OA of the hip and/or knee.

Acetaminophen

Historically, acetaminophen was used as a first-line agent for the treatment of mild to moderate pain in OA. The mechanism of action of acetaminophen is complex and includes both peripheral (COX 1 and 2 inhibition) and an independent central stimulation of descending serotonergic neuronal pathways, inhibition of L-arginine/NO pathway, stimulation of endocannabinoid system, and antinociception mechanisms [40].

The evidence to date suggests that NSAIDs are superior to acetaminophen for improving knee and hip pain in patients with OA [27]. In a Cochrane review, acetaminophen was inferior to NSAIDs in reducing pain and improving function in global assessments, but had a similar safety profile; both were better than placebo in outcomes [41]. Although there is no significant difference overall in the safety profiles between acetaminophen and NSAIDs, there are more adverse gastrointestinal events (RR 1.47, (95% CI 1.08 to 2.00) in patients taking NSAIDs [41].

In another meta-analysis, acetaminophen ((ES) 0.21, 95%CI 0.02 to 0.41) was less effective than NSAIDs ((ES) 0.20,95% CI 0.10 to 0.30) [42]. Overall, clinical improvement wasbetter with NSAIDs than with acetaminophen (RR = 1.24,95% CI 1.08 to 1.41). An overdose of acetaminophen canresult in severe liver injury and acute liver failure [43].Therefore, the limited efficacy and severe toxicity in overdose limit the use of acetaminophen in practice.

Duloxetine

Duloxetine is a serotonin-norepinephrine reuptake inhibitor and a centrally acting analgesic. It is an FDA-approved medication for pain control in OA, which significantly alleviates pain and improves function [29]. In a randomized doubleblind, placebo-controlled trial, duloxetine was effective as an adjunct treatment to oral NSAIDs for knee OA pain [30]. The group receiving the combination treatment reported additional pain relief and better function [30]. In a systematic review, combined analysis yielded the finding that 42% to 67% of subjects who took duloxetine reported ≥ 30% or ≥ 50% reduction in pain scores in OA [31]. In this analysis, the number needed to treat for duloxetine was 7, while the number needed to harm was between 16 and 19.

Capsaicin

Capsaicin is a naturally occurring compound found in chilies and is used as a topical preparation to alleviate pain [32]. It has some limited efficacy in pain reduction in OA without the benefits of improved function [44]. It could be used as an adjunct to other treatments, particularly when OA is limited to a single joint or a limited number of joints.

Opioids

Currently chronic long-term use of opioids is strongly discouraged due to the serious side effect profile [45]. The potential for tolerance, addiction, accidental overdose, and even death limit long-term opioid use. Moreover, chronic use of opioids may be associated with opioid-induced hyperalgesia [46]. Opioids should be prescribed only when necessary in the lowest effective dose and for the shortest duration in a carefully selected patient population [47].

Joint Modifying Treatments

Several drugs have been prescribed with the intention of slowing down, halting, or even reversing the joint damage caused by OA. Several preparations for disease-modifying treatments in OA are commonly used in the management of the disease (Table 2) [54]. These medications are usually well tolerated and have comparable efficacy to NSAIDs and acetaminophen.

Chondroitin and Glucosamine

Glucosamine and chondroitin, substances extracted from animal products, increase proteoglycan synthesis in articular cartilage [55]. Chondroitin, used in monotherapy or in a combination with glucosamine, is statistically more effective over a 6-month period and superior to placebo in alleviation of pain in patients with OA [48]. In a 6-monthlong, double-blind randomized trial, a combination of chondroitin sulfate and glucosamine showed efficacy comparable to celecoxib in subjects with severe pain from knee OA [49]. The combination was helpful in alleviating pain, improving functionality, increasing mobility, and reducing joint swelling [49].This combination also contributed to the statistically significant reduction in joint-space narrowing among subjects with symptomatic knee OA [56]. However, the treatment group did not show significant clinical improvement compared to placebo after a 2- year follow-up [56].

Table 2 Joint modifying treatments

Medication	Reference, year	Objetive	Subjects/participants	Design	Intervention	Control	Outcome
Chondroitin and glucosamine	Timothy et al., 2000	Evaluate the benefit of glucosamine and chondroitin for OA	Adults with OA in any joint.	Meta-analysis of RCT	Data extraction and scoring of trials using quality assessment Instrument	Placebo	QS ranged from 12.3 to 55.4% with a mean SD of 35.5% (12%). The total ES, 0.44 (95% CI, 0.24 –0.64) for glucosamine and 0.78 (95% CI, 0.60 –0.95) for chondroitin
	Jasvinder et al., 2015 [48]	Evaluate benefit of oral chondroitin for OA compared with placebo or traditional medication	N = 9110 with OA in any joint from 1 month to 3 years	Meta-analysis of RCT	Data from 43 RCT lasting longer than 2 weeks	Placebo	Reduction in knee pain by 20% in the chondroitin group versus 17% in the placebo group, an ARP of 6% (95% CI 1 to 11%)
	Hochberg et al., 2016 [49]	Efficacy of CS plus GH versus celecoxib in OA	N = 606 with moderate to severe knee OA pain	RCT	Patients randomized to receive 400 mg CS plus 500 mg GH or 200 mg celecoxib for 6 months	Celecoxib	The adjusted mean change (95% CI) in WOMAC pain was − 185.7 (− 200.3 to − 171.1) with CS + GH and − 186.8 (− 201.7 to − 171.9) with celecoxib, meeting the non-inferiority margin of − 40, − 1.11 (− 22.0 to 19.8; P = 0.92)
Intra-articular glucocorticoids	Arroll et al. 2004 [50]	Efficacy ofintra-articular glucocorticoid for OA of the knee	N = 41 trials	Meta-analysis of RCT	RR and NNT was assessed using the Jadad scoring system	Placebo	NNT was 4.4 with effectiveness seen at 16 to 24 weeks for higher doses of cortisone (equivalent to 50 mg prednisone)
	Faúndez et al., 2016 [51]	Effectiveness of intra-articular glucocorticoids	N = 810 patients	Meta-analysis of RCT	pain after 2 weeks and 3 months was assessed in all trials	Placebo	Pain was 1.5 cm on VAS with intra-articular glucocorticoids. SMD − 0.61 (− 0.78 to − 0.43)
Platelet-rich plasma	Patel et al., 2013 [52]	PRP provides symptomatic relief in OA of the knee	N = 78 patients with knee OA	RCT	Evaluated using the WOMAC questionnaire before treatment and at 6 weeks, 3 months, and 6 months	Placebo	Mean WOMAC scores at baseline were 10.18, 3.12, 36.56, and 49.86, respectively, and at final follow-up were 5.00, 2.10, 20.08, and 27.18, respectively, showing significant improvement (P < .001)
	Cole et al.,2017 [53]	Compare the clinical and effects of an intra-articular injection of PRP with those of an intra-articular injection of HA	N = 111 patients with symptomatic unilateral knee OA	RCT	WOMAC pain subscale, IKDC score and VAS for pain was assessed before and at 4 points across 1-year period of treatment	Placebo	IKDC score in the PRP group vs HA group at 54 weeks, (mean ± SE) 57.6 ± 3.37 vs 46.6 ± 3.76, P = .003 VAS score in the PRP group versus the HA group at 52 weeks (44 ± 4.6 vs 57.3 ± 3.8)

CI,confidence interval;CS, chondroitin sulfat; eES,effect size; GH, glucosamine hydrochlorid ;eHA, hyaluronicacid;IK DC,InternationalKneeDocumentation Committee; NN,Tnumberneededtotreat; PRP, platelet-rich plasma; QS, quality score; RR, relative risk; SD, standard deviation; SMD, standard mean difference; VAS, visual analog scale; Vs, versus; WOMAC, Western Ontario and McMaster Universities Arthritis Index

Key points

- Pain experience in OA is both peripheral and central in nature. Pain originates from nociceptive, inflammatory pathways and pain is exaggerated by central sensitization. Nocicepters in joints are stimulated by-
  - -Local inflammation
  - -Bone marrow lesions
  - - Neovascularization
  - -Structural bone changes such as remodeling
  - -And the new nerve generation in cartilage
  - -Menisci
  - -Osteophyte formation

Intra-Articular Steroids

Intra-articular steroids showed moderate efficacy in several short-term trials (up to 2 weeks), but no benefit in long-term use was indicated [50, 51]. A recent 2-year trial of intraarticular steroid use for knee OA showed that accelerated cartilage loss and pain improvement did not differ from saline injections [57]. These findings limit their use, except during acute exacerbation of OA.

Hyaluronic Acid

Hyaluronic acid (HA) is a naturally occurring fluid in joints that serves as a shock absorber and lubricant. Exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans, thereby preventing the degradation of cartilage and promote its regeneration [58]. The use of intraarticular HA is not supported as several studies showed no effect compared to intra-articular placebos. Eighteen large trials with a blinded outcome assessment showed a clinically irrelevant effect size of □ 0.11 (CI, □ 0.18 to □ 0.04) for HA in OA pain [59].

Platelet-Rich Plasma

Platelet-rich plasma (PRP) contains growth factors involved in tissue repair [60]. There is evidence to show that a single injection of PRP lessens pain and improves function and quality of life for 6 months [52]. In the study, PRP was superior to saline injections for pain, stiffness, and measures of functioning [52]. In another comparative trial of intra-articular PRP and HA, no difference was found in the primary outcome of pain scores [53]. Significant results were noted in secondary outcome measures, such as subjective wellness and reduction in pro-inflammatory markers supporting the use of PRP over HA [53].

There is minimal to non-existent evidence to support the use of HA, bisphosphonates, calcitonin, inducible NO synthase (iNOS) inhibitor, doxycycline and strontium in treatment of OA. None of these modalities improved joint-space narrowing, pain, or functioning [54, 59].

Biologics

Beyond the traditional pharmacological approaches discussed previously, several biological agents are under investigation for the treatment of OA (Table 3). These are genetically engineered proteins that target specific locations of the immune system and are very specific for their location of action.\

Anti-Nerve Growth Factor Monoclonal Antibodies

The use of monoclonal antibodies against nerve growth has shown benefits in the treatment of pain in OA. However, in 2010, the FDA placed a hold on all anti-NGF treatments due to concerns over rapidly progressive OA and osteonecrosis, even in non-target joints [66]. In 2015, after an extensive review, the hold was reversed [66]. Reversible paresthesia and dysthesia are the noteworthy side effects associated with higher doses of these medications [61].

Tanezumab is the most extensively studied monoclonal antibody for the treatment of OA. It shows greater efficacy when compared with opioids or NSAIDs with an EC of 0.23 CI 0.17–0.29) for pain index [62]. In the treatment of knee and hip OA, tanezumab is significantly more effective in improving both pain and physical function than NSAIDs [62]. The authors suggested that tanezumab monotherapy may provide a better treatment outcome, whereas NSAIDs are only partially effective in the treatment of OA pain [62]. In a metaanalysis, tanzezumab provided superior pain relief and improved function in patients with knee OA [63]. In a recent meta-analysis of ten randomized controlled trials, patients treated with tanezumab showed significantly better pain improvement, functional status and global assessment than the placebo group [67].

Tanezumab, fulranumab, and fasinumab demonstrated superiority to placebo in the treatment of knee and hip OA [61]. In a randomized double-blind trial of three doses (0.03, 0.1, 322 or 0.3 mg/kg) of fasinumab, all were better than placebo in improvement of knee pain and functional improvement in OA [64]. The use of anti-NGF monoclonal antibodies has provided a new dimension in the treatment of OA.

Other Antibodies

There are several ongoing clinical trials assessing the efficacy of a variety of antibodies against different cytokines and growth factors. Adalimumab and Tocilizumab, which target TNF and IL-6 respectively, are currently under investigation to treat pain in OA [68]. Similarly an anti-granulocyte macrophage colony stimulating factor antibody is being investigated for treatment of OA [65]

Table 3 Biologics

Medication	Reference, year	Objective	Subjects/ participants	Design	Intervention	Control	Outcome
Anti-NGF monoclonal antibodies	Schnitzer et al., 2015 [51]	Efficacy and safety of anti-NGF antibody in hip and knee OA	N = 8606 with OA knee or hip	Meta-analysis of RCT	Mean change in WOMAC pain and ES for tanezumab vs placebo	Placebo	ES from − 0.31 to 0.94 over a 20-fold dose range with heterogeneity (I2 = 42.6%, P = 0.14)
	Schnitzer et al., 2015 [52]	Benefit of tanezumab monotherapy replaced or co-administered with NSAIDs	N = 2700 with OA knee or hip	RCT	WOMAC pain and PGA for OA at baseline and 16 weeks	Placebo or NSAIDs	Significant improvements in WOMAC pain for tanezumab + NSAIDs versus NSAIDs alone
	Kan et al., 2016 [63]	Efficacy and safety of tanezumab for patients with knee OA.	N = 1839	Meta-analysis of RCT	WOMAC pain and PGA for OA reported as SMD	Placebo	Change in the WOMAC pain (SMD = 0.51, 95% CI 0.34 to 0.69, P < 0.00001) and PGA (SMD = 0.34, 95% CI 0.22 to 0.47, P < 0.00001)
	Tiseo et al., 2014 [64]	Efficacy offasinumab for OA of the knee	N = 217 Age 40–75 with OA	RCT	Pain intensity by WOMAC Index and TEAEs assessed	Placebo	TEAEs from 66.1 to 75.0% in the fasinumab groups vs 63.6% for placebo and improvement in WOMAC score
Novel agents	Cook et al., 2012 [65]	Effect of GM-CSF blockade in OA	GM-CSF-/-mice and wild-type (C57BL/6 mice		Treated with a monoclonal antibody to GM-CSF and pain development measured by weight distribution		Anti-GM-CSF mAb-treated mice had less arthritis in the lateral femur (P = 0.03) and medial femur (P = 0.004), compared with the control mAb-treated group

ES, effect size; GM-CSF, granulocyte monocytes-colony stimulating factor; mAB, monoclonal antibody; NGF, nerve growth factor; PGA, patients global assessment; SMD, standard mean difference; TEAEs, treatment emergent adverse effects; WOMAC, Western Ontario and McMaster Universities Arthritis Index

Key points

- Many non-pharmacologic and pharmacologic therapeutic modalities for the management of pain and improvement of function are currently in use, and other novel agents are being explored and developed. Due to the modest effects of the individual treatment options, a combination of therapeutic approaches is commonly used in practice.

Novel agents and future directions

Several novel agents, such as small moecules targeting ion channels and G protein-coupled receptors (GPCRs), are under investigation for treatment of pain in OA. Novel drugs that target the voltage-gated sodium channels NaV1.7 and NaV1.8 are under development for the treatment of OA pain [69]. Initial studies of NaV1.8, Strontium ranelate, recombinant human fibroblast growth factor 18 (sprifermin), and TRPV1 have shown some promising results [68]. Several other potentially therapeutic compounds, whose mechanism of action involves the cannabinoid receptors or selectively target δ, κ or μ opioid receptors, are currently undergoing clinical trials [68]. Researchers are trying to develop pain medications that provide central analgesia-like opioids, but without the risk of misuse or addiction [70].

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Surgical Management of Osteoarthritis of the Knee: Evidence-based Guideline

ABSTRACT :

Surgical Management of Osteoarthritis of the Knee: Evidencebased Guideline is based on a systematic review of the current scientific and clinical research. The guideline contains 38 recommendations pertaining to the preoperative, perioperative, and postoperative care of patients with osteoarthritis (OA) of the knee who are considering surgical treatment. The purpose of this clinical practice guideline is to help improve surgical management of patients with OA of the knee based on current best evidence. In addition to guideline recommendations, the work group highlighted the need for better research on the surgical management of OA of the knee.

Rationale

The American Academy of Orthopaedic Surgeons (AAOS), with input from representatives from the American Association of Hip and Knee Surgeons, the Arthroscopy Association of North America, the American Orthopaedic Society for Sports-Medicine, the Society of Military Orthopaedic Surgeons, the American Physical Therapy Association, the Society of Hospital Medicine, and the American Society of Anesthesiologists, recently published their clinical practice guideline (CPG), Surgical Management of Osteoarthritis of the Knee: Evidence-based Guideline. 1 The guideline contains 38 recommendations for improving the surgical treatment of patients with osteoarthritis (OA) of the knee based on current best evidence. This CPG was approved by the AAOS Board of Directors in December 2015, and has been officially endorsed by the American Association of Hip and Knee Surgeons, The Knee Society, the Society of Military Orthopaedic Surgeons, the American College of Radiology, the American Geriatrics Society, and the Arthroscopy Association of North America. The guideline uses the updated process and language changes to the AAOS CPG program approved by the AAOS Evidence-based Quality and Value Committee (EBQVC) in 2013.2 At the introductory meeting, the work group proposed population, intervention, control, and outcome (PICO) research questions for each area of interest. The work group used the expanded criteria for (1) research quality designations, (2) the concept of "best-available evidence synthesis," and (3) updated evidence rating categories and language. In the current AAOS guideline process, a consensus recommendation may be formulated by the work group if there is no supporting evidence and when not establishing a recommendation could have catastrophic consequences, such as loss of life or limb. No unanswered PICO questions fell into this category for this guideline. For the PICO questions with insufficient evidence to reach a conclusion, each query was forwarded on to an appropriate specialty society to serve as a potential area of future research.

The burden of OA of the knee is attributable to the effects of pain, stiffness, and disability, as well as the expense of treatment. Because the increasing prevalence ofOA of the knee is partly a function of the increase in the average age and the rate of obesity in the United States, OA is the most frequent cause of disability among adults in the United States.[3,4] In persons older than age 55 years, 10% have painful, disabling OA of the knee; of this group, one quarter are severely disabled.[5] In patients with arthritis, approximately 5% undergo surgery. Although these surgeries are costly, they are cost-effective in the longterm.[6,7] Arthroplasty of the knee is the most common reason for inpatient hospitalization, and 3 million women and 1.7 million men currently have undergone knee arthroplasty in the United States.[8]

To help improve surgical treatment of patients with OA of the knee based on the current best evidence, the AAOS leadership allocated resources to formulate an evidence-based CPG. The entire process adhered to the strict evidence-based CPG methodology developed by the AAOS; a member of the AAOS Committee on Evidence-based Quality and Value provided guidance by serving as an oversight chair. The work group formulated PICO questions that were designed to examine important and actionable interventions to create a clinically relevant document that addresses the surgical management of OA of the knee across the full episode of care. An extensive literature search was done to investigate these preliminary topics based on strict inclusion criteria designed to identify the best available evidence. Studies published in or after 1966 were included to ensure that no landmark studies were missed; however, most of the included studies were from the year 2000 and later. Using this time period best reflects advances in orthopaedic science and ensures that relevant, contemporary implants and techniques are being evaluated. The work group required that all studies have a sample size of at least 10 participants to limit the "small study" effect of lower-powered clinical trials. In the included studies, a minimum of 90% of patients had to have been diagnosed with OA of the knee; this was a compromise to avoid exclusion of valuable studies, and at the same time to ensure that inflammatory arthritis of the knee was not a primary diagnosis. The follow-up required in each study varied by PICO question, and was predetermined by the work group.

During the evidence analysis phase, 13,000 abstracts and more than 1,200 full-text articles were reviewed. The citations were

summarized, classified by patient outcomes, and graded by strength of methodology representing best available evidence to be used by the work group to formulate final evidence-based recommendations. A "best-available evidence synthesis" form of evidence analysis was employed, meaning that, although all studies that meet the inclusion criteria were examined, only the highest levels of available evidence were used. Retrospective series, small case series, and case reports were sometimes excluded because of the inherent risk of bias or because higher quality of evidence was available to address the same question. The use of this best evidence protocol reduces the adverse or favorable effect of poorly designed studies on the final recommendation.

The recommendations underwent a rigorous internal and external peer review process resulting in the final approved CPG. Seven peer reviewers, representing multiple specialty societies, submitted formal peer reviews. The work group carefully considered each reviewer's comments, responses were formulated and published, and changes were made as needed to the final document.

One theme that reviewers commented on was the inability to include stand-alone registry data and secondary research (ie, systematic and narrative reviews) as acceptable evidence. Currently, the only registry data acceptable for consideration in the CPG process are those published in the peer-reviewed literature. Retrospective analysis of registry data can lead to some of the flaws noted in observational research, namely bias, patient selection, and consecutiveness of reporting. Registries that embed prospective cohort studies within them are of acceptable quality for evidence-based analysis. For secondary research, analysts search through the bibliographies for any primary citations that meet the inclusion criteria. When appropriate, de novo metaanalyses are performed.

In summary, the guideline for surgical management of OA of the knee involved reviewing .13,000 abstracts and .1,200 full-text articles to develop 38 recommendations supported by 224 research articles meeting stringent inclusion criteria. Each recommedation is based on a systematic review of the research literature related to its topic which resulted in 14 recommendations classified as Strong, 14 as Moderate, and 10 as Limited. Strength of recommendation is assigned based on the quality of the supporting evidence.

Overview

To best impact patient care, pertinent highlights and limitations of the guideline recommendations are described so that they may be used in the appropriate context of the supporting evidence. Collectively, several themes emerge from these recommendations. Preoperative preparation with risk mitigation and rehabilitation is important for the best surgical outcomes. In addition, modern anesthesia and blood management techniques are helpful. Pros and cons exist about the use of unicompartmental knee arthroplasty (UKA) versus total knee arthroplasty (TKA) for isolated medial arthritis, as well as tourniquet usage and patellar resurfacing for TKA. No one fixation option has a strong advantage over another or for a cruciate-substitution design. In addition, no demonstrable advantages were shown for patientspecific instrumentation (PSI) or surgical navigation for routine TKA. Current evidence does not support the use of antibiotic-loaded bone cement, surgical drains, and continuous passive motion (CPM) machines. Finally, early postoperative mobilization and postoperative physical therapy are helpful for achieving the best outcomes.

Preoperative preparation with risk mitigation is important and safe. Strong evidence supports the finding that obese patients have less improvement in outcomes with TKA. Moderate evidence supports the findings that patients with diabetes mellitus are at a higher risk for complications and that patients with select chronic pain conditions have less improvement in patient-reported outcomes (PROs). Limited evidence supports the findings that patients with depression and/or anxiety have less improvement in PROs, patients with cirrhosis and hepatitis C are at a higher risk of complications, and supervised exercise before TKA may improve pain and physical function after surgery. Moderate evidence supports that a delay of 8 months prior to TKA does not worsen outcomes. These findings, when considered together, support the practice of optimizing the patient preoperatively when appropriate. For example, it is considered reasonable to delay surgery for up to 8 months to allow a morbidly obese patient to lose weight.9 Conversely, the recommendation does not

Key points

- The burden of OA of the knee is attributable to the effects of pain, stiffness, and disability, as well as the expense of treatment. Because the increasing prevalence of OA of the knee is partly a function of the increase in the average age and the rate of obesity in the United States, OA is the most frequent cause of disability among adults in the United States. In persons older than age 55 years, 10% have painful, disabling OA of the knee; of this group, one quarter are severely disabled.
- In patients with arthritis, approximately 5% undergo surgery. Although these surgeries are costly, they are cost-effective in the longterm. Arthroplasty of the knee is the most common reason for inpatient hospitalization, and 3 million women and 1.7 million men currently have undergone knee arthroplasty in the United States.

Key points

- To best impact patient care, pertinent highlights and limitations of the guideline recommendations are described so that they may be used in the appropriate context of the supporting evidence.
- Collectively, several themes emerge from these recommendations. Preoperative preparation with risk mitigation and rehabilitation is important for the best surgical outcomes.
- In addition, modern anesthesia and blood management techniques are helpful. Pros and cons exist about the use of unicompartmental knee arthroplasty (UKA) versus total knee arthroplasty (TKA) for isolated medial arthritis, as well as tourniquet usage and patellar resurfacing for TKA.

suggest that a delay in surgery, when a patient is otherwise ready, is necessary. As pointed out during peer review and commented on in the rationale for this recommendation, an unnecessary delay does not take into account the patient's pain and suffering nor does it address economic factors, such as loss of work.

Contemporary anesthesia and blood management techniques are supported. Strong evidence supports that both periarticular local anesthetic infiltration and peripheral nerve blockade for TKA decrease postoperative pain and opioid requirements. Moderate evidence supports that neuraxial anesthesia improves select perioperative outcomes and complication rates compared with general anesthesia. Strong evidence supports that treatment with tranexamic acid decreases postoperative blood loss and reduces the necessity of postoperative transfusions following TKA in patients with no known contraindications.

There are advantages and disadvantages of UKA versus TKA for isolated medial arthritis, as well as tourniquet usage and patellar resurfacing for TKA. Although limited evidence supports that partial arthroplasty may be used to decrease the risk of deep vein thrombosis and manipulation under anesthesia, moderate evidence supports that TKA may be used to decrease the number of revision surgeries. Regarding tourniquet usage, moderate evidence supports that a tourniquet decreases intraoperative blood loss, strong evidence supports that its use increases short-term postoperative pain, and limited evidence supports that its use decreases short-term postoperative function. Although strong evidence shows no difference in pain or function with or without patellar resurfacing in TKA, moderate evidence supports that patellar resurfacing in TKA may decrease cumulative revision surgeries after 5 years. Although these paired recommendations seem to be contradictory, they demonstrate that best evidence supports different outcomes depending on the intervention. Surgeons should use their judgment and patient preferences and values in determining the most appropriate surgical management.

No findings show a strong advantage regarding cruciate-substitution design, style of tibial component, or type of fixation. Strong evidence supports no difference in outcomes or complications between posterior-stabilized and posterior cruciate-retaining arthroplasty designs. Strong evidence supports use of either all-polyethylene or modular tibial components in knee arthroplasty because of no difference in outcomes. Strong evidence supports either cemented or noncemented tibial component fixation in TKA because of similar functional outcomes and rates of complications and revision surgeries. Moderate evidence supports the use of either cemented femoral and tibial components or noncemented femoral and tibial components in knee arthroplasty because of similar rates of complications and revision surgeries. Moderate evidence supports the use of either cementing all components or the use of hybrid fixation (ie, noncemented femoral component) in TKA because of similar functional outcomes and rates of complications and revision surgeries. Limited evidence supports the use of either all noncemented components or hybrid fixation (ie, noncemented femoral component) in TKA because of similar rates of complications and revision surgeries.

The use of navigation or PSI for routine TKA shows no demonstrable advantage. Strong evidence supports not using intraoperative navigation or PSI in TKA because no differences in outcomes or complications have been shown compared with conventional instrumentation. Moderate evidence supports not using PSI compared with conventional instrumentation for TKA because there is no difference in the rate of transfusions or complications. This wording is different than that seen in previous AAOS CPGs and reflects the 2013 CPG process update. In cases where an intervention, such as surgical navigation, is an additive procedure or technology, the wording "... evidence supports not using..." is employed to convey that the additive procedure or technology adds no benefit and should be avoided.

Drains, CPM, cryotherapy devices, and antibiotic-loaded bone cement are not supported. Strong evidence supports not using a drain with TKA because there is no difference in the rate of complications or outcomes. Likewise, strong evidence supports that the use of CPM after knee arthroplasty does not improve outcomes. Moderate evidence supports that the use of cryotherapy

devices after knee arthroplasty does not improve outcomes. Limited evidence does not support the routine use of antibiotic-loaded bone cement in primary TKA. Although there are times when these interventions are appropriate, this information will be discussed in the rationale section of each recommendation.

Early postoperative mobilization and preoperative and postoperative physical therapy are helpful to achieve the best outcomes. Strong evidence supports that rehabilitation started on the day of TKA reduces the length of stay in the hospital. Moderate evidence supports that rehabilitation started on the day of TKA, compared with rehabilitation started on postoperative day 1, reduces pain and improves function.Moderate evidence supports that initiation of a supervised exercise program during the first 2 months after TKA improves physical function. Limited evidence supports that a supervised exercise program initiated during the first 2 months after TKA decreases pain. Limited evidence supports that selected patients might be referred to an intensive supervised exercise program during the late stage (.2 months) after TKA to improve physical function.

In summary, this guideline is meant to elevate and standardize the current level of surgical care of patients with OA of the knee and stimulate additional research where there is currently a deficit or where experience and evidence are not in agreement. The CPG is a document that captures best surgical treatment evidence as of January 27, 2015. New data will undoubtedly emerge over time that clinicians will need to evaluate in order to adjust and optimize ongoing care for their patients.

The recommendations in this guideline are not intended to be a fixed protocol, and as with all evidencebased recommendations, practitioners must also rely on their clinical judgment and experience as well as their patients' preferences and values when making treatment decisions.

Recommendations

This summary of recommendations of the AAOS *Surgical Management of Osteoarthritis of the Knee: Evidence-based Guideline* contains a list of the evidence-based treatment and postoperative rehabilitation recommendations. Discussion of how each recommendation was developed and the complete evidence report are contained in the full guideline at www.orthoguidelines.org. Readers are urged to consult the full guideline for the comprehensive evaluation of the available scientific studies. The recommendations were established using methods of evidence-based medicine that rigorously control for bias, enhance transparency, and promote reproducibility.

This summary of recommendations is not intended to stand alone. Medical care should be based on evidence, a physician's expert judgment, and the patient's circumstances, values, preferences, and rights. For treatment procedures to provide benefit, mutual collaboration with shared decisionmaking between the patient and physician/allied healthcare provider is essential.

A Strong recommendation means that the quality of the supporting evidence is high. A Moderate recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong. A Limited recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Body Mass Index as a Risk Factor

Strong evidence supports that obese patients have less improvement in outcomes with TKA.
Strength of recommendation: Strong.

Diabetes as a Risk Factor

Moderate evidence supports that patients with diabetes are at a higher risk for complications with TKA.
Strength of recommendation: Moderate.

Chronic Pain as a Risk Factor

Moderate evidence supports that patients with select chronic pain conditions have less improvement in PROs with TKA.
Strength of recommendation: Moderate.

Depression/Anxiety as a Risk Factor

Limited evidence supports that patients with depression and/or anxiety symptoms have less improvement in PROs with TKA.
Strength of recommendation: Limited.

Key points

- Preoperative preparation with risk mitigation is important and safe. Strong evidence supports the finding that obese patients have less improvement in outcomes with TKA.
- Moderate evidence supports the findings that patients with diabetes mellitus are at a higher risk for complications and that patients with select chronic pain conditions have less improvement in patient-reported outcomes (PROs).
- Limited evidence supports the findings that patients with depression and/or anxiety have less improvement in PROs, patients with cirrhosis and hepatitis C are at a higher risk of complications, and supervised exercise before TKA may improve pain and physical function after surgery.

Key points

- In summary, this guideline is meant to elevate and standardize the current level of surgical care of patients with OA of the knee and stimulate additional research where there is currently a deficit or where experience and evidence are not in agreement.

Cirrhosis/Hepatitis C as a Risk Factor
Limited evidence supports that patients with cirrhosis or hepatitis C are at a higher risk for complications with TKA.
Strength of recommendation: Limited.

Preoperative Physical Therapy
Limited evidence supports that supervised exercise before TKA might improve pain and physical function after surgery.
Strength of recommendation: Limited.

Delay Total Knee Arthroplasty
Moderate evidence supports that a delay of 8 months prior to TKA does not worsen outcomes.
Strength of recommendation: Moderate.

Periarticular Local Anesthetic Infiltration
Strong evidence supports the use of periarticular local anesthetic infiltration compared with placebo in TKA to decrease pain and opioid use.
Strength of recommendation: Strong.

Peripheral Nerve Blockade
Strong evidence supports that peripheral nerve blockade for TKA decreases postoperative pain and opioid requirements.
Strength of recommendation: Strong.

Neuraxial Anesthesia
Moderate evidence supports that neuraxial anesthesia may be used in TKA to improve select perioperative outcomes and complication rates compared with general anesthesia.
Strength of recommendation: Moderate.

Tourniquet Use and Blood Loss Reduction
Moderate evidence supports that the use of a tourniquet in TKA decreases intraoperative blood loss.
Strength of recommendation: Moderate.

Tourniquet Use and Postoperative Pain Reduction
Strong evidence supports that the use of a tourniquet in TKA increases short-term postoperative pain.
Strength of recommendation: Strong.

Tourniquet Use and Postoperative Function
Limited evidence supports that the use of a tourniquet in TKA decreases short-term postoperative function.
Strength of recommendation: Limited.

Tranexamic Acid
Strong evidence supports that treatment with tranexamic acid decreases postoperative blood loss and reduces the necessity of postoperative transfusions following TKA in patients with no known contraindications.
Strength of recommendation: Strong.

Antibiotic Bone Cement
Limited evidence does not support the routine use of antibiotic bone cement for primary TKA.
Strength of recommendation: Limited.

Cruciate-retaining Arthroplasty
Strong evidence supports no difference in outcomes or complications between posterior-stabilized and posterior cruciate-retaining arthroplasty designs.
Strength of recommendation: Strong.

Polyethylene Tibial Component
Strong evidence supports use of either all-polyethylene or modular tibial components in knee arthroplasty because of no difference in outcomes.
Strength of recommendation: Strong.

Patellar Resurfacing: Pain and Function
Strong evidence supports no difference in pain or function with or without patellar resurfacing in TKA.
Strength of recommendation: Strong.

Patellar Resurfacing: Revision Surgery
Moderate evidence supports that patellar resurfacing in TKA may decrease cumulative revision surgeries after 5 years compared with no patellar resurfacing in TKA.
Strength of recommendation: Moderate.

Cemented Tibial Components Versus Noncemented Tibial Components
Strong evidence supports the use of cemented or noncemented tibial component fixation in TKA as a result of similar functional outcomes and rates of complications and revision surgeries.
Strength of recommendation: Strong.

Cemented Femoral and Tibial Components Versus Noncemented Femoral and Tibial Components
Moderate evidence supports the use of either cemented femoral and tibial compo-

nents or noncemented femoral and tibial components in knee arthroplasty because of similar rates of complications and revision surgeries.
Strength of recommendation: Moderate.

All-cemented Components Versus Hybrid Fixation
Moderate evidence supports the use of either cementing all components or hybrid fixation (ie, noncemented femoral component) in TKA as a result of similar functional outcomes and rates of complications and revision surgeries.
Strength of recommendation: Moderate.

All Noncemented Components Versus Hybrid Fixation
Limited evidence supports the use of either all noncemented components or hybrid fixation (ie, noncemented femoral component) in TKA as a result of similar rates of complications and revision surgeries.
Strength of recommendation: Limited.

Bilateral Total Knee Arthroplasty
Limited evidence supports simultaneous bilateral TKA in patients aged #70 years or American Society of Anesthesiologists status 1-2, because there is no increased rate of complications.
Strength of recommendation: Limited.

Unicompartmental Knee Arthroplasty Revision Surgery
Moderate evidence supports that TKA could be used to decrease the risk of revision surgery compared with UKA for OA of the medial compartment.
Strength of recommendation: Moderate.

Unicompartmental Knee Arthroplasty: Deep Vein Thrombosis and Manipulation Under Anesthesia
Limited evidence supports that UKA might be used to decrease the risk of deep vein thrombosis and manipulation under anesthesia compared with TKA for OA of the medial compartment.
Strength of recommendation: Limited.

Unicompartmental Knee Arthroplasty Versus Osteotomy
Moderate evidence supports no difference between UKA or valgus producing proximal tibial osteotomy in outcomes and complications in patients with OA of the medial compartment.
Strength of recommendation: Moderate.

Surgical Navigation
Strong evidence supports not using intraoperative navigation in TKA because there is no difference in outcomes or complications.
Strength of recommendation: Strong.

Patient-specific Instrumentation: Pain and Function
Strong evidence supports not using PSI compared with conventional instrumentation for TKA because there is no difference in pain or functional outcomes.
Strength of recommendation: Strong.

Patient-specific Instrumentation: Transfusions and Complications
Moderate evidence supports not using PSI compared with conventional instrumentation for TKA because there is no difference in transfusions or complications.
Strength of recommendation: Moderate.

Drains
Strong evidence supports not using a drain with TKA because there is no difference in complications or outcomes.
Strength of recommendation: Strong.

Cryotherapy Devices
Moderate evidence supports that the use of cryotherapy devices after knee arthroplasty do not improve outcomes.
Strength of recommendation: Moderate.

Continuous Passive Motion
Strong evidence supports that CPM after knee arthroplasty does not improve outcomes.
Strength of recommendation: Strong.

Postoperative Mobilization: Length of Stay
Strong evidence supports that rehabilitation started on the day of TKA reduces the length of hospital stay.
Strength of recommendation: Strong.

Postoperative Mobilization: Pain and Function
Moderate evidence supports that rehabilitation started on the day of TKA compared with rehabilitation started on postoperative day 1 reduces pain and improves function.
Strength of recommendation: Moderate.

Key points

- This summary of recommendations is not intended to stand alone. Medical care should be based on evidence, a physician's expert judgment, and the patient's circumstances, values, preferences, and rights.
- For treatment procedures to provide benefit, mutual collaboration with shared decision making between the patient and physician/allied healthcare provider is essential. A Strong recommendation means that the quality of the supporting evidence is high.
- A Moderate recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the quality/applicability of the supporting evidence is not as strong.

Key points

- A Limited recommendation means that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm.

Early-stage Supervised Exercise Program: Function
Moderate evidence supports that a supervised exercise program during the first 2 months after TKA improves physical function.
Strength of recommendation: Moderate.

Early-stage Supervised Exercise Program: Pain
Limited evidence supports that a supervised exercise program during the first 2 months after TKA decreases pain.
Strength of recommendation: Limited.

Late-stage Postoperative Supervised Exercise Program: Function
Limited evidence supports that selected patients might be referred to an intensive supervised exercise program during late-stage postoperative TKA to improve physical function.
Strength of Recommendation: Limited.

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■ **Alberto Magni , Piergiuseppe Agostoni , Cesare Bonezzi , Giuseppe Massazza , Paolo Mene, Vincenzo Savarino , Diego Fornasari**

Management of Osteoarthritis: Expert Opinion on NSAIDs

ABSTRACT: Osteoarthritis (OA) is a leading cause of disability among older adults worldwide. Treatment aims are to alleviate inflammatory pain and improve physical function through non-pharmacological and pharmacological interventions. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapy. However, selection is challenged by patient age, comorbidities and polypharmacy, and by the drug's benefit/risk balance, all of which together influence the risk of cardiovascular (CV), gastrointestinal (GI) and renal adverse events (AEs). While the efficacy profile of the various NSAIDs is delineated, the differences in their safety profile are not straightforward. This narrative review provides practical indications by a multidisciplinary Italian expert panel for general practitioners and specialists managing OA patients with chronic inflammatory pain; the goal is to maximize therapy efficacy while reducing untoward effects caused by inappropriate NSAID use. The discussion on the best approach to NSAIDs spanned the following topics: (1) patient evaluation: investigate pain origin, duration and components together with possible risk factors for CV, GI and renal AEs; (2) non-pharmacological interventions: the physiatrist provides a person-centered, holistic approach accounting for all patient aspects; (3) pharmacological interventions: patient profile and drugs' pharmacological properties affect NSAID selection, which drugs to be used in combination or to be avoided, formulation and therapy duration; (4) the pharmacologist's, general practitioner's and pain therapist's points of view; (5) NSAID safety: the individual baseline risk and the drug's safety profile are major determinants of CV, GI and renal risk; consider possible drug–drug interactions; (6) periodical re-evaluation of treatment response and adherence, using scales to assess pain and function.

Keywords: Chronic inflammatory pain; Clinical practice; Non-steroidal anti- inflammatory drugs; Osteoarthritis; Safety

INTRODUCTION

Osteoarthritis (OA) is the most frequent form of arthritis worldwide and a leading cause of disability among older adults [1]. In Italy, its prevalence is 24.9% in women and 16% in men and is highest in persons aged [85 years (63.0% in women and 50.9% in men) [2, 3]. After hypertension, it is the second most common chronic disease managed by general practitioners (GPs) [2].

The main risk factors for OA are age, gender, obesity and adverse mechanical factors [4]. Knees, hips and hands are the most commonly affected appendicular joints, and patients often suffer from pain, stiffness, swelling and loss of normal joint function, with a negative impact on their quality of life and a relevant socioeconomic burden.

The goal of treatment in OA is to reduce pain intensity and improve function and quality of life through a combination of non-pharmacological and pharmacological interventions [5, 6]. As first-line therapy, guidelines [4–8] recommend the non-steroidal anti-inflammatory drugs (NSAIDs), a chemically heterogneous group of agents that inhibit the production of prostaglandins (PG) and thromboxane A through the blockade of cyclooxygenase (COX). Traditional NSAIDs (tNSAIDs), which target the COX-1 and COX-2 isozymes to varying degrees, have a consolidated role in the symptomatic treatment of pain in musculoskeletal disorders [9–11], but their long-term use is limited by toxicity, mainly cardiovascular (CV), gastrointestinal (GI) and renal toxicities. Although COX-2-selective NSAIDs (coxibs) were initially introduced as a safer alternative to tNSAIDs, their use has been associated to a high risk of CV events [12].

The frequent, inappropriate use of over-the counter NSAIDs is a matter of concern as it rises the risk of untoward events [13–15]. According to a recent Italian long-term active pharmacovigi-lance study, NSAIDs are responsible for 8.4% of the emergency department visits and 24.4% of emergency department visits resulting in hospitalizations [16].

In practice, both drugs' and patients' characteristics influence the choice of therapy. The efficacy profile of NSAIDs has been delineated by meta-analyses of randomized controlled trials (RCTs) [17–23]. Among these, the network meta-analysis by da Costa and colleagues, comparing the effectiveness of various NSAIDs, paracetamol and placebo on pain and physical function improvement, included the highest number of preparations and doses and provided also information on the dose–response relation [21]. It included 74 RCTs, for a total of 58,556 OA patients. Overall, there was not enough statistical evidence to support the superiority of diclofenac 70 mg/day, naproxen 750 mg/day and ibuprofen 1200 mg/day over placebo for pain and physical function improvement. In contrast, for pain reduction, diclofenac 150 mg/day and etoricoxib given at 30 mg/day, 60 mg/day and 90 mg/day had a probability of reaching the minimum clinically important difference compared to placebo of C 95%, reaching 100% only in the case of diclofenac 150 mg/day and etoricoxib 60 mg/day. Notably, a significant linear dose–effect response was found only for celecoxib (P = 0.030), diclofenac (P = 0.031) and naproxen (P = 0.026). As for the physical function

Key points

- Osteoarthritis (OA) is the most frequent form of arthritis worldwide and a leading cause of disability among older adults. In Italy, its prevalence is 24.9% in women and 16% in men and is highest in persons aged [85 years (63.0% in women and 50.9% in men). After hypertension, it is the second most common chronic disease managed by general practitioners (GPs). The main risk factors for OA are-
  - -Age
  - -Gender
  - -Obesity
  - -Adverse mechanical factors

improvement, a minimum clinically important treatment effect was observed solely for diclofenac 150 mg/day. The authors concluded that diclofenac at 150 mg/day is the best NSAID in terms of both pain and function amelioration in OA, superior to the maximum doses of frequently used NSAIDs, including ibuprofen, naproxen and celecoxib. Albeit etoricoxib at the maximum dose of 60 mg/day was as effective as diclofenac 150 mg/day for the treatment of pain, its effect estimates on physical disability remain unclear. Finally, paracetamol had no clinical effect and should not be recommended for the symptomatic treatment of OA. This study demonstrates that the same NSAID at different doses has different effects and provides important information on the minimal effective dosages of a number of compounds [21].

While the efficacy profile of the various NSAIDs is clear, the differences in their safety profile are not straightforward and are affected by individual characteristics [20, 24]. In the last 10 years, several meta-analyses of RCTs and observational studies have compared the safety profile of these drugs [20, 25–33]. Yet, study design and endpoints are heterogeneous [24], and data are biased, for instance, by the fact that they often rely on prescriptions rather than on actual administrations (i.e. no consideration of the exposure duration and dose) without accounting for the reason for the prescription, nor for concomitant diseases and risk factors. For some compounds, the lack of robust data from large cohort studies may be mistakenly regarded as a guarantee of safety.

To support healthcare providers in the optimization of OA patient management, i.e. trying to maximize therapy efficacy while reducing untoward effects caused by inappropriate NSAID use [14], a multidisciplinary expert panel (i.e., 1 GP, 1 pharmacologist, 1 pain therapist, 1 cardiologist, 1 gastroenterologist, 1 nephrologist and 1 physiatrist) thoroughly discussed the best approach in this complex setting. To inform the group's discussion, a literature search was performed via PubMed using the following items as the main keywords: "NSAID," "osteoarthritis," "chronic pain," "effectiveness," "efficacy," "safety," "cardiovascular," "gastrointestinal" and "renal." We limited the search to articles in English. Electronic Supplementary Material (ESM) Table 1 presents the systematic reviews and/or meta-analyses of RCTs and observational studies on NSAID efficacy and safety published in the past 10 years and included in the present work. This work is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

This narrative review summarizes the main messages and practical indications for GPs and specialists.

CHRONIC PAIN

Definition of Chronic Pain

The term ''chronic'' refers to a pain persisting over time (according to the Internation-al Association for the Study of Pain [IASP], chronic pain either persists or recurs for [3 months [34]) but provides no details on whether the stimuli persist or if other patho-genetic mechanisms intervene. Certainly, pain persistence affects patients' life and complicates their clinical status.
For some investigators, "chronic" implies the involvement of the central nervous system, where pathogenetic mechanisms able to maintain chronicity even in the absence of peripheral stimuli develop. Others believe that "chronic" relies on the occurrence of nervous mechanisms typical of neuropathic pain and refer to it as to a mixed or neuropathic-like pain.

There are degenerative and neurological disorders characterized by chronic injuries and in which pain is induced chronically (erythromelalgia, fibromyalgia, deafferentation pain, OA, rheumatoid arthritis [RA], etc.). Many conditions are accompanied by episodes of pain of variable persistence that affects distinct parts of the body over time.

Finally, pain could be defined as chronic if it is not effectively treated or if it is related to undiagnosed diseases.

Types of Chronic Pain

The IASP describes three types of pain: nociceptive, neuropathic and nociplastic [34]. Nociceptive pain is of inflammatory or degenerative origin depending on the presence or absence of a mechanism of nociceptor sensitization. Inflammatory pain starts in the tissue nociceptive nerve endings and represents the type of chronic pain experienced

by patients with OA. The responsible mechanism, i.e. peripheral sensitization, consists in a threshold reduction at the peripheral ends of the sensory nerve fibers, which become responsive to low-intensity stimuli (i.e. allodynia) or may even become spontaneously active. Peripheral sensitization depends on biochemical modifications of nociceptive fibers triggered by mediators of inflammation, such as PGs and cytokines. If the sensitizing agents are removed, the biochemical processes revert, and the normal threshold is re-established.

Neuropathic pain is classified as peripheral or central, based on the site of injury and, thus, of the ectopic activity: the site of pain origin is along the somatosensory pathway affected by a disease or a lesion (from peripheral nociceptors to central neurons). Other definitions, such as neuropathic-like pain, neuropathic component and mixed pain, are frequently associated to nociceptive pain to underline a central component of pain (spinal cord sensitization) that becomes responsible for neuropathic symptoms. It cannot be considered a real neuropathic pain because of the lack of neurological deficit signs.

PATIENT EVALUATION

The Diagnostic Work-Up

Osteoarthritis is a heterogeneous disease with distinct phenotypes [35]. Before commencing a therapy with NSAIDs, it is fundamental to

(1) Collect all relevant clinical information to define the disease characteristics, clinical status and possible risk factors for OA, with par ticular attention to pain description, psychosocial aspects, comorbidities and risk of CV, GI and renal complications.

(2) Perform the I- and II-level assessments as per current guidelines [4].

Pain Assessment

As a first step in pain assessment, the GP must define the pain type, as NSAIDs are effective against inflammatory nociceptive pain but not against non-inflammatory mechanical–structural pain (occurring in approximately 10–15% of OA patients). To infer the type of pain (i.e. somatovisceral or neurological condition), symptoms should be measured using the scales for neuropathic pain, keeping in mind that many symptoms are typical of both types of pain. The most used tools to discriminate neuropathic pain from non-neuropathic pain in clinical settings include painDETECT [36], the Leeds assessment of neuropathic symptoms and signs Pain Scale [37] and the Douleur Neuropathique 4 questions [38]; all of these tools rely on the description of pain and on the bedside examination of sensory dysfunction. Moreover, painDETECT has been recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials to screen for neuropathic pain phenotypes [39]. Although these scales are easy to use and allow a preliminary clinical assessment, they are considered to be useful screening tools and cannot replace a thorough clinical assessment and their accuracy varies across different populations [40, 41].

When considering the pathogenetic mechanisms, it is appropriate to investigate whether the pain is localized, evoked, radiating or referred (by identifying the pain area and inspecting it, evoking pain with non-painful stimuli and testing skin sensitivities), as well as the negative symptoms, which predominate at the sites of neuropathic pain. The following tools should be employed: the generic and unidimensional pain assessment tools Visual Analogue Scale (VAS) and Numeric Rating Scale (NRS), to rapidly and easily measure pain intensity [42]; the Western Ontario and McMaster Universities Arthritis Index (WOMAC), to measure arthritis symptoms, pain and physical functional disability specifically in patients with OA of the knee and the hip [43]. Both the VAS and NRS are self administered and can detect changes over time [42]. The NRS may be preferred over the VAS because of its simpler score calculation and because it may be administered both verbally and in writing, while the VAS can be administered only in writing. However, due to their nature, they do not provide a comprehensive pain evaluation in patients with rheumatic disease [42]. As for the WOMAC, it is one of the most appropriate patient-reported outcome measures to be employed in trials of knee and hip OA; however, interpretation of the results and comparisons among studies are frequently challenged by the different versions available (Likert, VAS or NRS) and by the wide variation in its use and analysis [44, 45].

Key points

- Knees, hips and hands are the most commonly affected appendicular joints, and patients often suffer from pain, stiffness, swelling and loss of normal joint function, with a negative impact on their quality of life and a rele vant socioeconomic burden.
- The goal of treatment in OA is to reduce pain intensity and improve function and quality of life through a combination of non-pharmacological and pharmacological interventions.

Key points

- As first-line therapy, guidelines recommend the non-steroidal anti-inflammatory drugs (NSAIDs), a chemically heterogneous group of agents that inhibit the production of prostaglandins (PG) and thromboxane A through the blockade of cyclooxygenase (COX).

A definitive diagnosis is made by combining the clinical and neurophysiological evaluations with the diagnostic nerve block test.

Often, in a context of degenerative pain, patients experience periods of inflammation. The test of the response to NSAIDs (acting on PGs) and cortisone (acting on cytokines) may be helpful, but it must follow—not replace—the clinical evaluation. PGs and cytokines act by sensitizing the peripheral nociceptive endings, i.e. increasing their responsiveness to stimuli below the normal threshold. PGs are the first mediators of inflammation released during the inflammatory process that follows the injury, while cytokines are released later on. When performing the test, it is important to keep in mind that the central analgesic activity of certain NSAIDs may interfere with the result.

Function and patient global assessment (PGA) of disease severity have to be assessed as well. The most frequently used tools are the WOMAC, VAS or Likert scales and global function score for function and the VAS or 5-point Likert scale for PGA of disease severity.

Atypical Presentation

In case of atypical presentation, imaging is recommended to confirm the diagnosis of OA and/ or make alternative or additional diagnoses [4]. Radiological imaging allows potential changes in bone, cartilage and inflammation to be monitored [35] and includes cartilage evaluation to verify possible interjoint space reduction, increased density of subchondral bone and abnormal reactive growth of the bone at the edge of joint (osteophytes). Conventional radiography is the gold standard.

Table 1 The main factors that increase the risk of cardiovascular, gastrointestinal and renal complications to be considered before starting a therapy with non-steroidal anti-inflammatory drugs in patients with osteoarthritis

Main risk factors for NSAID-associated AEs		
CV	GI	Renal
Age	Past complicated ulcer	Older age
Gender	Multiple NSAIDs, including ASA	Risk of dehydration
Smoking	Concomitant anti-coagulants, ticlopidine and clopidogrel	Frequent need for contrast media radiologic diagnostic procedures
Comorbidities (e.g. hypertension, diabetes, obesity, heart failure, CVD)	Past-uncomplicated ulcer	Comorbidities
		Atherosclerosis
Concomitant therapies (e.g. diuretics, antibiotics, nephrotoxic drugs, low-dose ASA)	Age[65 years]	CVD (e.g. chronic heart failure)
		Liver cirrhosis
Hospitalization	Steroids	Chronic glomerular disease
Lifestyle		Nephrotic syndrome Diabetes
Use of OTC NSAIDs Hyperlipidemia		Hypertension
Coronaropathy		NSAID-related allergy
Cerebrovascular disease		
Peripheral Vasculopathy		Concomitant therapies
COPD		ACE-inhibitors
Concomitant antiaggregant therapy		ANG II-receptor antagonists
		High-dose diuretics

ACE Angiotensin-converting-enzyme, AEs adverse events, ANGangiotensin,ASA acetylsalicylic acid, COPDchronic obstructive pulmonary disease,CV cardiovascular,CVD cardiovascular disease,GI gastrointestinal,NSAIDsnon-steroidal anti-inflammatory drugs,OTC over-the-counter

Differential Diagnosis

It is important to exclude RA and other types of chronic arthritis in OA patients. According to the updated recommendations of the Italian Society of Rheumatology, laboratory tests (blood count, inflammation, urinalysis or synovial fluid) should be performed for OA patients with marked inflammatory symptoms and/or signs, especially when atypical sites are involved, for differential diagnostic purposes, particularly to exclude chronic or crystal-induced arthropathies [4].

Comorbidities and Risk Assessment

During the visit and before starting the chosen therapy with NSAIDs, GPs should consider the conditions at the highest risk of potental complications upon NSAID treat-ment and verify the presence of a number of important factors that increase the risk of CV, GI, and renal adverse events (AEs) (Table 1):

(1) Prior CV events (major acute myocardial infarction [AMI], stroke, peripheral venous and arterial thrombosis). The CV risk should be calculated using the European Soci - ety of Cardiology score [46]; however, in outpatient practice, it is rarely calculated and is frequently overlooked, although it is a key determinant of the choice of the most appropriate treatment option. Patients are considered at high risk when the score of the 10-year fatal CV disease (CVD) risk is 5–10% or if they have familial dyslipidemia, severe hypertension, diabetes without CV risk factors and organ damage or moderate chronic renal failure [46, 47].

(2) GI intolerance (abdominal pain, constipation, diarrhea, dyspepsia and nausea) an major GI events (e.g. perforation and bleeding, which depends on age and comorbidities [48]).

(3) Kidney function: diseases like acute kidney failure, interstitial nephritis and chronic kidney failure should be considered. A thorough screening and a complete labora tory work-up should be undertak en for each patient at risk of renal AEs based on age, comorbidities such as diabetes and chronic re nal failure and concurrent antihy pertensive therapies (anti-angio tensin [ANG] II, anti-aldosterone treatment).

The patient must be educated on lifestyle and prevention.

The panelists agreed that the ideal pathway for OA patients suffering from chronic inflammatory pain is the process illustrated in Fig. 1

When to Consult the Pain Therapist

It is necessary to refer a patient to a pain center if:

(1) The origin of pain was not identified (lack of pathogenetic diagnosis).

(2) The pharmacological treatment was not successful. The pain ther apist should be consulted before referring the patient to specialists and before administering opioids.

(3) Treatment reduced pain but not disability.

(4) The patient presented intolerance or contraindications to NSAIDs.

Practical Indications

(1) During the visit, pain must be thoroughly evaluated, considering:
- pain origin and duration
- component (inflammatory or

Key points

- Traditional NSAIDs (tNSAIDs), which target the COX- 1 and COX-2 isozymes to varying degrees, have a consolidated role in the symptomatic treatment of pain in musculoskeletal disorders, but their long-term use is limited by toxicity, mainly cardiovascular (CV), gastrointestinal (GI) and renal toxicities. Although COX-2-selective NSAIDs (coxibs) were initially introduced as a safer alternative to tNSAIDs, their use has been associated to a high risk of CV events.

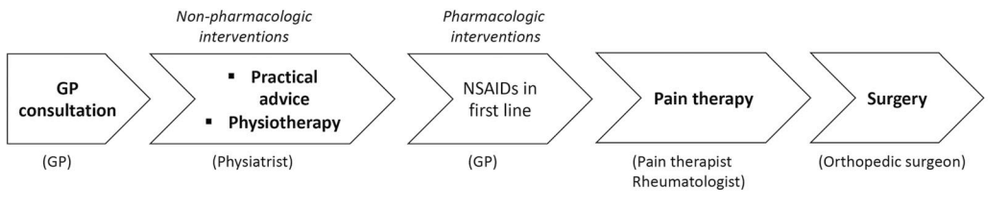

Fig. 1 The ideal pathway for osteoarthritis patients suffering from chronic inflammatory pain. GP General practitioner, NSAIDs non-steroidal anti-inflammatory drugs

Key points

- Neuropathic pain is classified as peripheral or central, based on the site of injury and, thus, of the ectopic activity:
  - The site of pain origin is along the somatosensory pathway affected by a disease or a lesion (from peripheral nociceptors to central neurons).
  - Other definitions, such as neuropathic-like pain, neuropathic component and mixed pain, are frequently associated to nociceptive pain to underline a central component of pain (spinal cord sensitization) that be comes responsible for neuropathic symptoms.
  - It cannot be considered a real neuropathic pain because of the lack of neurological deficit signs.

degenerative)
- NSAID activity (peripheral or central)

(2) Consider possible factors that increase the risk of CV, GI and renal AEs.
(3) Calculate the CV risk.
(4) Prescribe a complete laboratory work-up, including serum chloride measurement, to test the kidney function.

NON-PHARMACOLOGICAL THERAPY

Orthopedic Treatment, Supplements, and Physiotherapy

In the setting of OA, beyond pharmacological therapy, it is important to consider specific orthopedic treatments (surgical and non-surgical), use of dietary supplements and physiatrist assessment, especially for rehabilitative interventions and supplemental physical therapies.

The specialist in orthopedics and traumatology is a surgeon and, as such, should be consulted to determine whether a patient suffering from OA may benefit from a surgical approach. In all the other cases, the reference specialist is the physiatrist, who takes charge of OA patients and makes a prospective evaluation of their functional needs. Once the patient has been evaluated, the physiatrist makes an individual rehabilition plan to estimate the functional aspects as well as rehabilitative prognosis.

Role of the Physiatrist

In first place is the GP, who prescribes I-level instrumental/imaging examinations (i.e. radiography and musculoskeletal ultrasound) for OA patients before a surgical consultation with the orthopedic surgeon. The physiatrist will then take charge of the patient and design the individual rehabilitation project (i.e. "the set of propositions, elaborated by the rehabilitation team, coordinated by the medical doctor specialist") [49]. This represents the basis of a person-centered, holistic approach that accounts for the individual conditions globally: indeed, it includes the main scales of motor, cognitive and social assessments characterizing the clinical history of the patient. The physiatrist is the leader of the rehabilitation team that takes charge of patients undergoing or not undergoing surgery.

Based on the individual rehabilitation project, the physiotherapist sets up the individual rehabilitation program aimed at achieving the therapeutic objectives established in the individual rehabilitation project.

Rehabilitation Therapies and Physical Exercises

The prerequisite to optimization of the process of care for OA patients is pain reduction/treatment. Physical antalgic therapies, similar to minimally invasive interventional treatments (i.e. intra- or extra-articular injections), represent an integral part of the rehabilitative approach, with its rationale built into the individual rehabilitation project.

OA causes a reduction in the mechanical functioning and overall clinical status. Most patients suffering from OA are frail with several comorbidities, and thus the physiatrist consults with other specialists, including neurologists, geriatrists, anesthesiologists, internists, among others. Sarcopenia and frailty increase the risk of falls, leading to the need for a broader range of therapeutic strategies, including adequate diet and exercise, to support OA patients.

Practical Indications

(1) Use functional scales for the clinical assessment. Consider
(2) consulting a physiatrist during the post-operative rehabilitation.
(3) Account for all patient aspects.
(4) Pay close attention to prevent falls and the sequelae of reduced mobility caused by OA.

PHARMACOLOGICAL THERAPY: NSAIDS

The Pharmacology of NSAIDs

Rationale for the Use of NSAIDs in OA

In case of inflammation, NSAIDs can switch off peripheral sensitization by inhibiting a relevant amount of PGs. Thus, their use as first-line therapy aimed at treating inflammatory nociceptive pain is virtually always appropriate; however, the feasibility of such strategy depends on the condition of the patient.

Conversely, the use of paracetamol (very

common in OA although it is not an NSAID) is inappropriate in inflammatory pain, since it is a weak inhibitor of COX-1 and a very weak inhibitor of COX-2 and, as such, it does not interfere with peripheral sensitization. In addition, in tissues with inflammation, the free radicals inactivate paracetamol, abolishing any action on COX-2 [50]. In line with these observations, its analgesic effect cannot depend on COX inhibition. Paracetamol is actually a central analgesic with multiple effects, the main one being the stimulation of the endogenous cannabinoid system [51]. Hence, paracetamol has a lower efficacy than NSAIDs in reducing inflammatory pain [21] and its central analgesic efficacy is also lower than that of opioids.

Are All NSAIDs Equal?

All NSAIDs have an inhibitory activity on COX1 and COX-2 but there are several differences among NSAIDs (for details on the mechanisms of action of the most common NSAIDs refer to [52–54]) that impact on their efficacy and safety [54]. These include:

- Chemical similarity
- COX isoform selectivity and potency [55].

NSAIDs comprise non-selective drugs, such as ibuprofen and naproxen, and selective COX-2 inhibitors (i.e. coxibs), such as etoricoxib and celecoxib. Potency is not a synonym of selectivity and cannot be used to predict dosages: a drug is potent if it inhibits 50% of available COX-1 and COX-2 at low dose. For example, etoricoxib is a selective inhibitor of COX-2 but it is less potent than diclofenac which, together with ketorolac (which has no indication in OA treatment), is the most potent inhibitor of COX-2 [55]. Importantly, the kinetics of COX-1 and COX-2 inhibition are different (non-linear and linear, respectively [56]). In clinical practice, to achieve a significant anti-thrombotic effect through the blockade of thromboxane A synthesis, 95–97% of platelet COX-1 must be inhibited. If 90% of the enzyme is blocked, no anti-thrombotic effect occurs. The only NSAID able to inhibit 95% of COX-1 is acetylsalicylic acid (ASA), which irreversibly blocks the enzyme and, if administered at the dose of 100 mg per day every day, maintains this level of inhibition. No other NSAID is able to produce this effect, with the exception of naproxen but at non-conventional doses and regimens. Thus, it is not completely true that NSAIDs alone interfere with platelet function. Certainly, there are COX-1-independent antiplatelet effects that may play a role. NSAIDs induce mostly GI bleeding as they block COX-1 in surface epithelial cells. Given in concomitance with other drugs, such as the selective serotonin reuptake inhibitors, the antiplatelet effects of NSAIDs are enhanced.

- Plasma half-life. This feature impacts on the occurrence of AEs. Indeed, the NSAIDs inhibiting gastric COX-1 for a longer time are more harmful for the stomach. For example, piroxicam and diclofenac have a half-life of about 60 and 1 h, respectively, but the latter is a more potent inhibitor of COX-1 and is associated to a relative risk of gastric bleeding of 3.61 compared to 8.00 for piroxicam [57].
- Interference with ASA. Not all NSAIDs interfere with the cardioprotective effects of ASA. Diclofenac, ketorolac and etoricoxib do not, but they are the most potent inhibitors of COX-2 and, thus, of the endothelial prostacyclin (PGI2) production. Upon ASA treatment, the levels of thromboxane A drop and only the endogenous PGI2 remain, leading to a "thrombotic equilibrium." If COX-2 is blocked, the equilibrium is impaired again. Ibuprofen, but not etoricoxib or diclofenac, seems to interfere with the capability of ASA to irreversibly acetylate platelet COX-1. This might reduce the protective effect of ASA against the risk of atherothrombotic events. Notably, combining ASA (required to prevent CV events) with a coxib may enhance the protective effect of COX-2 inhibition toward the gastric mucosal and prolong the time to recover from gastric mucosal injury [58]. According to the pharmacologist, patients on ASA must not take any NSAID. In particular cases, such as of a gout flare or of a renal colic, they may take such therapy for 1–2 days.
- Penetration into the synovial liquid. Not all NSAIDs adequately penetrate into the synovial liquid (e.g. ibuprofen does not while diclofenac does), so even in the case of a short half-life, the higher the absorption at the synovial site, the longer the pharmacological effect [59].
- Passage through the blood–brain barrier. This aspect related to the central action of NSAIDs may be of interest when selecting the most appropriate drug. Some compounds, such as diclofenac, pass through the barrier and reach the spinal cord, where the PGs produced by neurons and astroglia play a role in central sensitization. Therefore, at this site, inhibition of COX-1 and COX-2 adds to the

Key points

- As a first step in pain assessment, the GP must define the pain type, as NSAIDs are effective against inflammatory nociceptive pain but not against non-inflammatory mechanical–structural pain (occurring in approximately 10–15% of OA patients).
- To infer the type of pain (i.e. somatovisceral or neurological condition), symptoms should be measured using the scales for neuropathic pain, keeping in mind that many symptoms are typical of both types of pain.

Key points

- In case of atypical presentation, imaging is recommended to confirm the diagnosis of OA and/ or make alternative or additional Diagnoses.
- Radiological imaging allow-spotential changes in bone, cartilage and inflammation to be monitored and includes cartilage evaluation to verify possible interjoint space reduction, increased density of subchondral bone and abnormal reactive growth of the bone at the edge of joint (osteophytes). Conventional radiography is the gold standard.

peripheral effect (possible synergism) so that the analgesic activity resulting from the anti-inflammatory action adds to a central analgesic effect occurring when high drug doses reach the central nervous system.

Factors Influencing the Individual Response to NSAIDs

Several players affect the inter-patient variability observed in the response to NSAID therapy:

(1) Genetic variations in the enzymes that metabolize NSAIDs (cyto chrome P450 2C9 [CYP2C9] in many cases) and COXs.

(2) The microbiota, for its capability to inactivate drugs. However, data in this regard are scarce.

(3) The possibility of phenotyping OA (e.g. coxarthrosis vs. gonarthrosis), which is rather concrete [35] and may help to decide if and how to use an NSAID therapy—the choice should rely on the evidence from head-to-head comparisons or network meta-analyses [19–21].

(4) Gender, which is responsible for relevant differences in the incidence, prevalence and prognosis of several immunoinflammatory diseases. Pre-clinical studies have demonstrated that the molecular mechanisms of inflammation and pain may differ between men and women. All of these differences provide a plausible background to understand why women use more NSAIDs than men. However, the pharmacological mechanisms underlying the gender-driven NSAID responses remain elusive[60].

By When Should We Expect the Response to NSAID treatment?

Usually, the maximum peak plasma concentration is reached within 2–3 h of administration, but the efficacy also depends on other factors (e.g. plasma protein binding and tissue distribution with particular regard to the inflammatory osteoarticular tissue). The rapid effect is pain reduction, which is achieved also through the central activity of NSAIDs; the delayed effect is the reduction of inflammation and thus the rise of the threshold; the variable effect is the improvement in disability. The analgesic effect occurs within about 1 week and the full anti-inflammatory effect is often achieved in 3 weeks (which questions the 3-day test validity, as the specificity is very low) [61]. A recent study has shown that the NSAID-induced improvement in pain and function peaks at 2 weeks and starts to decline by 8 weeks, while minor CV and GI AEs occur as early as 4 weeks after the initiation of NSAID treatment [62].

What is the Adequate Duration of NSAID Therapy?

In general, NSAIDs should be used for the shortest duration possible and at the lowest dose that guarantees both inflammation reduction and physical function improvement, as established in efficacy studies [21, 61]. Therapy duration must be tailored to the patient profile [61]. Usually, the treatment duration is at least 7–10 days, taking into account the time required to achieve both the analgesic and full anti-inflammatory effects [61]. If at the end of the 3-week period no result has occurred, a switch to another agent should be attempted [61].

Monotherapy or Combination Therapy?

It is possible to combine NSAIDs with central analgesics, such as paracetamol and opioids. By targeting different mechanisms, such combinations permit the dose to be limited, thus reducing the risk of AEs. In contrast, the combination of NSAIDs with steroids should be avoided: in fact, although they are very effective against inflammation and cause only marginal gastric erosion in subjects without risk factors, these drugs delay the healing of possible microulcers, highly enhancing the NSAID-induced gastric erosion. In this context, the number of administrations plays a central role.

General Considerations on the Different Formulations

Oral intake through the direct contact between drugs and the GI tract mucosa increases the likelihood of topical damage until absorption. Topical formulations are usually preferred over systemic treatments for safety reasons, such as in patients aged [75 years [4, 5]. In patients with comorbidities, to favor compliance, formulations relying on one or few administrations (e.g. modified release) should be considered.

Practical Indications

(1) Avoid the use of paracetamol in case of inflammatory pain.

(2) NSAIDs should be used for the

shortest duration and at the lowest dose that guarantees the effect on inflammation and improve ment in physical function.

(3) Define therapy duration based on the patient profile and avoid the on-demand use of NSAIDs: in the case of inflammatory pain, therapy must be administered for at least 10 days to achieve analgesia and for 3 weeks to achieve the full anti-inflammatory effect.

(4) It is possible to combine NSAIDs with central analgesics such as paracetamol and opioids.

(5) Avoid the combination of NSAIDs with steroids.

(6) Consider formulations relying on one or few administrations to improve adherence.

Making Sense of NSAID Therapy: The Specialists' Point of View

In clinical practice, in-depth knowledge of each NSAID's efficacy and safety profile, together with the patient characteristics, is critical to define the benefit/risk balance of each compound for a specific individual and drive the therapeutic choice.

Table 2 summarizes the considerations made by the GP, the pharmacologist and the pain therapist of the multidisciplinary panel.

The Safety Profile of NSAIDs

The main AEs that may occur upon NSAID therapy are illustrated in Fig. 2.

NSAIDs and CV Risk

NSAID-Related CV AEs The CV safety of NSAIDs is a very controversial matter. Following the observation that NSAIDs could increase the risk of CV events at therapeutic doses or higher, in 2005 the U.S. Food and Drug Administration added a black box warning to their use [63], while the European Medicines Agency decided to contraindicate coxibs (but not tNSAIDs [64]) in patients with coronary heart disease or stroke and to advise those at risk for coronary heart disease to use these agents with caution [65].

The possible mechanisms proposed to explain CV complications include (1) the unbalance between the vasodilator effect of PGI2 and PGE2 in favor of vasoconstriction by thromboxane A2 in the endothelium, which results in a prothrombotic effect; and (2) sodium and water retention promoted by COX inhibition, which worsens heart failure, hypertension and ventricular remodeling.

The Coxib and Traditional NSAID Trialists' (CNT) Collaboration meta-analysis is the largest meta-analysis on NSAID safety, based on 639 RCTs in which tNSAIDs/coxibs were used for long periods [26]. It investigated the vascular effects of coxibs (celecoxib, etoricoxib and lumiracoxib) and high-dose tNSAIDs (diclofenac, ibuprofen and naproxen) in older patients with rheumatic diseases [26]. Coxibs, diclofenac and ibuprofen displayed a similar relative risk for CV events (range 1.37–2.49), whereas naproxen did not seem to increase it (range 0.39–1.87). Coxibs, diclofenac and ibuprofen also displayed a comparable annual absolute risk for major vascular events, which varied according to the baseline predicted risk: in lowrisk subjects, the predicted absolute risk of major vascular events was low regardless of the NSAID administered (2 per 1000 in all cases for coxibs, diclofenac and ibuprofen; 0 per 1000 for naproxen); in high-risk patients, the risk increased and was similar for high-dose diclofenac and coxibs (8 per 1000 and 7 per 1000, respectively) and possibly ibuprofen (9 pe 1000), while it seemed to be lower for high-dose naproxen (- 1 per 1000). [26]. A subsequent network meta-analysis found no difference in the risk of major CV events with diclofenac, ibuprofen, naproxen, celecoxib and etoricoxib for the treatment of pain in patients with OA or RA [20].

The PRECISION trial, conducted in subjects with OA or RA at increased CV risk and treated with celecoxib, naproxen and ibuprofen, showed a similar number of CV-related deaths, nonfatal myocardial infarction (MI) or nonfatal stroke among the three groups of NSAIDs, but ibuprofen and naproxen had been used at doses and for periods not in line with guidelines [66].

The absolute risk for CV effects increases to a greater extent in patients with or at risk for active atherosclerotic processes (e.g. with recent bypass surgery, unstable angina or ischemic cerebrovascular events) receiving a COX inhibitor. The excess number of events depends on the underlying risk of the patient, the relative risk of the drug and the duration of the followup [58].

Key points

- It is important to exclude RA and other types of chronic arthritis in OA patients.
- According to the updated recommendations of the Italian Society of Rheumatology, laboratory tests (blood count, inflammation, urinalysis or synovial fluid) should be performed for OA patients with marked inflammatory symptoms and/or signs, especially when atypical sites are involved, for differential diagnostic purposes, particularly to exclude chronic or crystal-induced arthropathies.
- During the visit and before starting the chosen therapy with NSAIDs, GPs should consider the conditions at the highest risk of potental complications upon NSAID treatment and verify the presence of a number of important factors that increase the risk of CV, GI, and renal adverse events (AEs)

Table 2 Considerations driving the choice of therapy according to the general practitioner, the pharmacologist and the pain therapist

The pharmacologist's point of view	The GP's point of view	The pain therapist's point of view
1. The main indication for NSAIDs is inflammatory nociceptive pain, while their use is not appropriate in other forms of pain.	Once the patient characteristics have been defined, there are 4 fundamenta drug features that drive the choice toward a particular NSAID therapy:	Drug efficacy is defined according to the available data on established efficacy and safety outcomes (see section Patient Evaluation)
2. In some OA patients, central sensitization may play an important part in pain persistence. Thus, it is often useful to combine NSAIDs with paracetamol or opioids, as they are active on central synapses. When opioids are given, it is important to know the modalities of discontinuation and to monitor patients during both opioid and NSAID therapy.	1. The efficacy profile in OA 2. The safety profile in terms of risk of CV events, GI bleeding and nephrotoxicity 3. The interference with concomitant therapies, particularly ASA and oral anticoagulants 4. The formulation (e.g. extended release), which is a key determinant of patient compliance	In particular, when evaluating the efficacy of NSAID therapy, use scales for both pain and function
3. Frequently, a pharmacological treatment is more effective if associated to rehabilitation and minimally invasive techniques, which should not be considered as the last step in the process of care.	However, it must be stressed that the choice is not straightforward because of the lack of clear-cut evidence (see section on safety)	

GP General practitioner,OA osteoarthritis

Key points

- In the setting of OA, beyond pharmacological therapy, it is important to consider specific orthopedic treatments (surgical and non-surgical), use of dietary supplements and physiatrist assessment, especially for rehabilitative interventions and supplemental physical therapies.

A recent meta-analysis of individual patient data in real-world settings [30] has shown that all traditional NSAIDs are associated with an increased risk of AMI, similar to that reported with celecoxib therapy. Using a high daily dose (celecoxib [200 mg, diclofenac [100 mg, ibuprofen [1200 mg, naproxen [750 mg) for 8–30 days was associated with the greatest risk, which did not increase further beyond the first 30 days. Based on these findings, prescribers should consider weighing the risks and benefits of NSAIDs before selecting the treatment, particularly for higher doses.

In patients with a prior MI, the excess risk of mortality has been estimated to be approximately six deaths per 100 person-years of treatment with a COX-2 inhibitor compared with no NSAID treatment [67]. A Danish largescale study based on national administrative registers and conducted in healthy individuals demonstrated an increased risk for death/MI in diclofenac and celecoxib users (hazard ratio [95% confidence interval] vs. non-users: 1.63 [1.52–1.76] and 2.01 [1.78–2.27], respectively), which increased in a dose-dependent fashion [68]. Moreover, in low-risk patients, an increased risk of pooled CV events was found with lower doses of diclofenac versus paracetamol, ibuprofen and naproxen (which, however, varied based on the event considered) over 1 month; surprisingly, the relative risk decreased in patients at high CV risk [69], but the explanation remains unclear [24]. Finally, the SOS project, which included millions of Europeans, showed a similar modest increase in CV risk with diclofenac and other NSAIDs, compared to

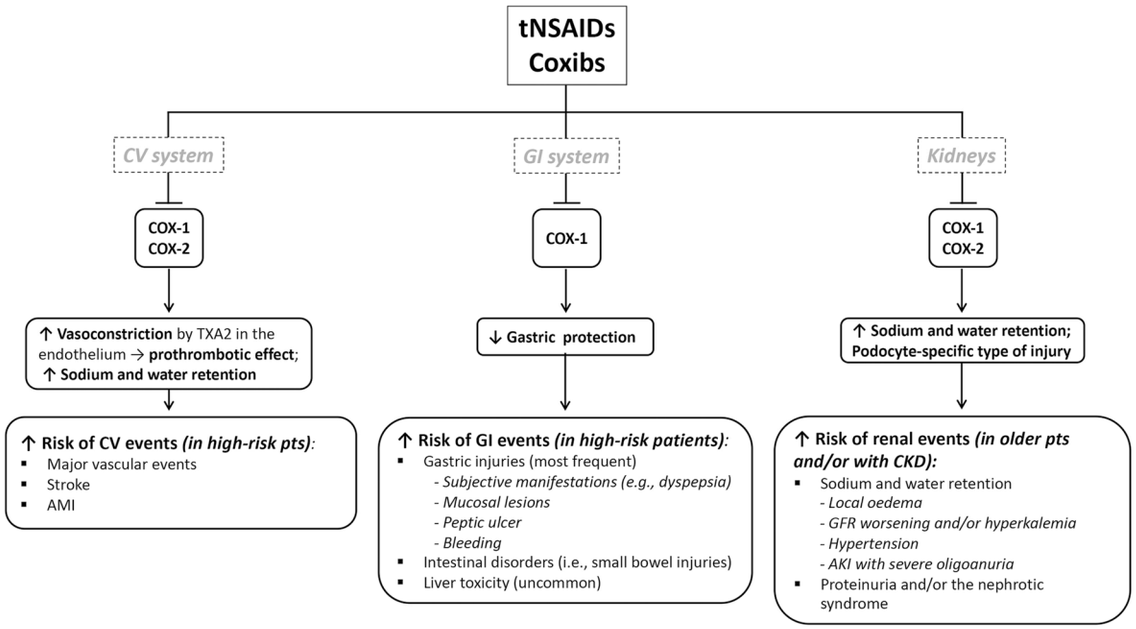

Fig. 2 The main adverse events observed in osteoarthritiscoxibs COX-2 inhibitors, CV cardiovascular, GFR patients upon NSAID therapy (see text for discussion). glomerular filtration rate, GI gastrointestinal, tNSAIDs AKI Acute kidney injury,AMI acute myocardial infarc- traditional non-steroidal anti-inflammatory drugs, TXA2 tion, CKD chronic kidney disease, COX cyclooxygenase, thromboxane A2

non-use [70]. Nonetheless, bias linked to the design of the available studies do not allow definitive conclusions to be drawn.

A recent study showed that patients on anticoagulant therapy with both vitamin K antagonists and dabigatran should avoid NSAIDs due to a greater risk of hemorrhage, especially GI bleeding, and more frequent complications (such as strokes and embolisms) [71]. The use of NSAIDs has always been discouraged in patients receiving antivitamin K therapy, but this is valid advice also for those who receive dabigatran and likely all direct anticoagulants. No specific data are currently available for rivaroxaban, edoxaban and apixaban.

Finally, it must be pointed out that the concomitant administration of certain NSAIDs weakens the protective CV effects of ASA [72–74]. Co-administration of ibuprofen in patients with documented CVD on low-dose ASA therapy significantly increased the risk of all-cause and CV mortality (hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.30–2.87; HR 1.73, 95% CI 1.05–2.84, respectively) compared to ASA alone [72]. No difference was observed when diclofenac or other NSAIDs were used with ASA versus ASA alone [72].

In conclusion, the main determinant of the risk of AEs is the patient profile. A slight increase in CV risk occurs mainly in case of high doses and long-term use, which, however, are not recommended by current guidelines. The only indication to limit the CV risk is to adhere to the recommended dosages and duration and, possibly, undergo cycles of therapy with periodical interruptions.

Practical Indications

(1) In patients with a prior MI, extra caution is needed in the use of NSAIDs/coxibs.

(2) Use only the recommended doses and for the shortest period neces sary to control or relieve symptoms.

(3) Monitor renal function and blood pressure in NSAID/coxib users, especially if they

Key points

- The physiatrist will then take charge of the patient and design the individual rehabilitation project (i.e. "the set of propositions, elaborated by the rehabilitation team, coordinated by the medical doctor specialist").

Key points

- All NSAIDs have an inhibitory activity on COX1 and COX-2 but there are several differences among NSAIDs (for details on the mechanisms of action of the most common NSAIDs refer to that impact on their efficacy and safety. These include:
  - Chemical similarity
  - COX isoform selectivity and potency.
- NSAIDs comprise non-selective drugs, such as ibuprofen and naproxen, and selective COX-2 inhibitors (i.e. coxibs), such as etoricoxib and celecoxib. Potency is not a synonym of selectivity and cannot be used to predict dosages: a drug is potent if it inhibits 50% of available COX-1 and COX-2 at low dose.
- For example, etoricoxib is a selective inhibitor of COX-2 but it is less potent than diclofenac which, together with ketorolac (which has no indication in OA treatment), is the most potent inhibitor of COX-2.

present preexisting conditions such as hypertension, renal disease and heart failure [75].

NSAIDs and GI Risk

NSAID-Related GI AEs Non-steroidal antiinflammatory drugs-induced GI AEs are various and sometimes severe even though their prevalence is not high [16]. The most frequent GI AEs assocated with NSAID therapy are gastric injuries, which range from subjective manifestations, such as dyspepsia, to ulcers with complications. In elderly patients with arthritis, the incidence of GI intolerability AEs was reported to be significantly lower with celecoxib (16.7%) than with naproxen (29.4%; P \ 0.0001), ibuprofen (26.5%; P = 0.0016) and diclofenac (21.0%; P \0.0001). The discontinuation rate due to these AEs was similar for celecoxib (4.0%) and diclofenac (4.2%; P = 0.75) and significantly lower than for naproxen (8.1%; P \ 0.0001) and ibuprofen (7.3%; P \ 0.05) [76].

Up to 70% of NSAID users experience minimal mucosal lesions as early as within a few hours of intake [77]; these may indicate gastric mucosa frailty and the tendency to become real ulcers [78]. NSAID-induced ulcer, mainly gastric, is becoming more and more frequent due to the increased use of these drugs, especially in the elderly. As NSAID use and *Helicobacter pylori* are two independent determinants of ulcer development, they may have additive effects on the ulcer risk in the same subject. Thus, the most recent international guidelines recommend that patients be tested for the presence of the infection and, if present, to eradicate it in those who have to start a prolonged therapy with NSAIDs [79]. The most frequent ulcer complication is bleeding, with a rate ratio (RR) of 1–2% per year. The underlying disease seems to be important: for example, the rate of bleeding is 1.3–2% per year in RA patients and 0.7–10% per year in those with OA [80].

NSAID users may also experience intestinal disorders, including small bowel injuries [77], which may be caused by the mucosal inflammatory pathway triggered by microbiota changes [81].

Liver toxicity events are much less frequent than gastric injuries. Paracetamol used at high doses, at least 4 g per day, may damage the liver [82]. Other studies found that the RR of liver damage defined by hypertransaminasemia was higher for nimesulide (2.2) and sulindac (5) than for diclofenac (1.5) [82].

Most of the patients who develop a serious GI AE while on NSAID therapy are asymptomatic prior to the event [83], particularly the elderly. Among the risk factors for the onset of NSAID-associated ulcer complications (Table 1), advanced age is a primary risk factor for GI events [84]: indeed, NSAID users aged 75–- 89 years have a twofold higher risk of bleeding (RR 4.1) compared to users aged 60–74 years (RR 2.0) [85]. It is frequent to observe, in the emergency department, elderly patients who use NSAIDs chronically and present severe anemia with hemoglobin levels of 4–5 gr/dl without having ever experienced any dyspeptic symptom. Therefore, physicians must check their patients periodically for the presence of anemia (fecal occult blood test, hematocrit) and symptoms associated with this condition (headache, asthenia, dyspnea, etc.). Conversely, many patients with troublesome symptoms (e.g. epigastric pain and dyspepsia) may have a normal endoscopy at the upper GI tract [86]. As for steroids increasing the risk of complications, it must be pointed out that, when used alone, they do not represent an actual risk for ulcerogenesis [87]

The type of non-selective NSAID impacts on the frequency of GI damage. The results from two epidemiological studies have led to establish a scale of risk for different tNSAIDs (i.e. ibuprofen, diclofenac, naproxen, ketoprofen, indomethacin, piroxicam and azapropazone); azapropazone and piroxicam were associated to the highest risk of gastroduodenal bleeding (odds ratio [OR] 23.4–31.5 and 13.7–18, respectively) and diclofenac and ibuprofen with the lowest (OR 3.9–4.2 and 2.0–2.9, respectively) [88, 89]. Table 3 presents the results from two recent meta-analyses of RCTs that report the rate of risk for bleeding associated with tNSAIDs and coxibs versus placebo [26] and for major GI events associated with tNSAIDs and coxibs versus diclofenac [20]. In particular, the CNT meta-analysis reported that the annual absolute risk of upper GI complications for coxibs, diclofenac, ibuprofen and naproxen depended on the baseline risk [26]. Both in patients at low and high risk, diclofenac and coxibs yielded a similar risk (in low-risk patients: 2 per 1000; in high-risk patients: 6 per 1000, respectively) that was lower than that of ibuprofen and naproxen (in low-risk

Table 3 Risk of gastroduodenal bleeding or overall gastrointestinal complications according to the NSAID administered

NSAID	CNT Collaboration meta-analysis [26][a]	Van Walsem et al. [20][b]
Ibuprofen	3.63 (1.09–12.12)	0.5 (0.3–0.9)
Diclofenac	2.20 (1.06–4.54)	-
Naproxen	5.49 (2.74–10.99)	0.3 (0.2–0.6)
Coxibs[c]	2.22 (1.16–4.23)	-
Celecoxib	-	1.4 (0.8–2.3)
Eterocoxib	-	1.5 (1.3–1.9)

coxib Cyclooxygenase 2 (COX-2)-selective NSAIDs,CELECoxib and Traditional NSAID Trialists a Data are expressed as rate ratio (RR) with the 95% confidence interval (CI) in parentheses vs. placebo b Data refers to major GI events, not only bleeding, which are expressed as the RR with the 95% CI in parentheses vs. diclofenac (i.e., a RR \ 1 favors diclofenac and[1 favors the comparator) c Celecoxib, etoricoxib, rofecoxib, lumiracoxib

patients: 4 per 1000; in high-risk patients: 15 and 16 per 1000, respectively), in line with the results from previous epidemiological studies [88, 89].

Among the NSAID features that may impact on gastrolesivity, plasma half-life plays a major role. A study conducted in elderly subjects [90] evaluated the presence of gastroduodenal bleeding through the measurement of fecal blood loss and found that it was higher with drugs with a longer plasma half-life, such as naproxen (2.76 ml fecal blood loss) and piroxicam (1.16 ml), compared to diclofenac (0.53 ml), a NSAID with a shorter half-life, and placebo (0.28 ml). Other factors responsible for a different gastrolesive effect among NSAIDs are the level of pK (higher levels increase the toxic effect) and the dosage.

When is it Adequate to Use Proton Pump Inhibitors with NSAIDs in the Prevention of NSAID-Induced Damage? Non-steroidal anti-inflammatory drug-induced GI damage can be significantly reduced by increasing the gastric pH through the administration of proton pump inhibitors (PPIs), which are the most potent acid inhibitors available. Unlike H2-antagonists that prevent only the onset of duodenal ulcers, PPIs can protect both the stomach, the main site of NSAID-induced damage, and the duodenum [91]. The protective action of PPIs depends on the fact that the weakening of the mechanisms of mucosal defense induced by NSAIDs implies that even a reduced amount of acid, such as in the case of the chronic gastritis that is always associated to gastric ulcers, may be dangerous [92]. A number of important risk factors must be considered due to the need to administer an appropriate prophylactic therapy with PPIs [93] (Table 4).

PPIs have to be administered throughout the period of NSAID use; even half the standard dose seems to be sufficient to achieve the benefit [94].

Practical Indications

(1) There are no dietary or behavioral suggestions to prevent or reduce
(2) NSAID-induced GIlesions. When selecting a NSAID, in high-risk patients or in case of prolonged therapy duration, compounds with the lowest risk of GI events should be preferred.
(3) The optimal treatment duration depends on the disease and corresponds to the period of acute symptoms or of functional joint impairment.
(4) Use PPIs in the presence of particular risk factors.

NSAIDs and Renal AEs

NSAID-Induced Renal and Reno-Vascular Events and Risk Factors the untoward effects of NSAIDs is the inhibition of endogenous or inflammatory renal PGs, a subfamily of eicosanoids. Endogenous eicosanoids fine-tune renal microcirculation and water and electrolyte transport across renal tubules. PGs, such as PGE1 and 2 or PGF2a, control sodium reabsorption and the concentration/dilution mechanism. Likewise, endothelial PGI2 and platelet thromboxane A2 balance

Key points

- The PRECISION trial, conducted in subjects with OA or RA at increased CV risk and treated with celecoxib, naproxen and ibuprofen, showed a similar number of CV-related deaths, nonfatal myocardial infarction (MI) or nonfatal stroke among the three groups of NSAIDs, but ibuprofen and naproxen had been used at doses and for periods not in line with guidelines.

Key points

- Among the NSAID features that may impact on gastrolesivity, plasma half-life plays a major role. A study conducted in elderly subjects evaluated the presence of gastroduodenal bleeding through the measurement of fecal blood loss and found that it was higher with drugs with a longer plasma half-life, such as naproxen (2.76 ml fecal blood loss) and piroxicam (1.16 ml), compared to diclofenac (0.53 ml), a NSAID with a shorter half-life, and placebo (0.28 ml).
- Other factors responsible for a different gastrolesive effect among NSAIDs are the level of pK (higher levels increase the toxic effect) and the dosage.

each other to control vascular tone in glomeruli and renal arterioles, including the vasa recta. As this counterbalance mechanism is marginal in the normal kidney, NSAID inhibitors of eicosanoid biosynthesis have very modest effects in the healthy kidney and/ or younger individuals and are usually well tolerated in persons with normal renal function.

Elderly individuals or patients with chronic kidney disease (CKD) are likely to experience at least some mild AEs, ranging from local edema (e.g. hands, lower limbs, water retention with rapid weight gain) to worsening of glomerular filtration rate (GFR) and/or hyperkalemia. This is usually more frequent in patients with certain comorbidities: in particular, in hypertensive subjects NSAID therapy may lead to intensification of anti-hypertensive regimen [95]. The effects are usually reversible but tend to synergize with other agents affecting renal function, such as anti-hypertensive drugs. In selected circumstances, acute kidney injury (AKI) may occur with severe oligoanuria. A meta-analysis of observational studies [28] found a statistically significant elevated AKI risk in patients treated with indomethacin, piroxicam, ibuprofen, naproxen and sulindac versus non-users, with pooled RRs ranging from 1.58 to 2.11. In all other cases (i.e. diclofenac, meloxicam, and celecoxib), the increase in AKI risk was not significant. Another meta-analysis of observational studies [29] reported that, in the general population, the pooled OR of AKI for ongoing NSAID exposure was 1.73 (95% CI 1.44–2.07) and was higher in older people (OR 2.51, 95% CI 1.52–2.68); in people with CKD, it was 1.63 (95% CI 1.22–2.19) and ranged from 1.12 to 5.25. Notably, the risk was higher for NSAIDs with no COX-2 selectivity (OR 1.84, 95% CI 1.54–2.19) and decreased with increasing COX2 selectivity (C 5-fold, OR 1.41, 95% CI 1.07–1.87).

Various NSAIDs have been implicated in glomerular disorders leading to proteinuria and/ or the nephrotic syndrome, possibly due to some podocyte-specific type of injury [96]. In other instances, interstitial nephritis can occur bacause of NSAID immuno-allergic effects that are most likely unrelated to COX inhibition [97]. Under most circumstances, proteinuria or non-oliguric AKI rapidly disappear upon therapy discontinuation.

Another issue that may impact on the renal adverse effects of NSAIDs is the lack of apparent recognition of renal dysfunction by prescribing physicians. Notably, sudden changes of GFR may go unnoticed if serum creatinine, blood urea nitrogen or serum K? are not measured during NSAIDs therapy. Thus, the real prevalence of renal untoward effects of NSAIDs may be largely underestimated. A recent systematic review [98] noted a cross-sectional point prevalence of NSAID use of between 8 and 21% in 49,209 patients with CKD, demonstrating that despite guidelines recommending against their use, a substantial proportion of CKD patients continue to receive NSAIDs.

NSAIDs and Arterial Pressure The pro-hypertensive effects of NSAIDs are believed to stem from three major mechanisms [99]:

(1) Na? and Cl- retention and in creased antidiuretic hormone mediated water reabsorption at the distal collecting duct
(2) Blockade of the vasodilator effects of PGE2 and PGI2 on the kidney microcirculation
(3) Unbalanced activity of the renin/ angiotensin/aldosterone axis, nor mally regulated by local vascular and tubular eicosanoid biosynthesis.

No effect on blood pressure (BP) has been observed in ASA [100–102] and coxib users [103, 104]. Among non-selective NSAIDs, ibuprofen and indomethacin—but not diclofenac—were shown to increase the risk of hypertension in arthritis patients [103]. In a metaanalysis of 19 RCTs including 45,000 patients with arthritis treated for[4 weeks with COX-2 inhibitors, non-selective NSAIDs or placebo, coxibs caused a weighted mean difference point estimate increase in systolic and diastolic BP compared with placebo and non-selective NSAIDs, and were associated with a non-significantly higher RR of causing hypertension compared with placebo and non-selective NSAIDs [105]. Another meta-analysis of 49 RCTs with 130,000 patients—mostly with arthritis— found that coxibs caused greater hypertension than either non-selective NSAIDs or placebo after at least 4 weeks of treatment. However, the effect was heterogeneous, with a marked BP increase in etoricoxib users and a slight effect in users of celecoxib, valdecoxib and lumiracoxib [106]. The review did not report absolute risk changes or provide numbers

needed to treat or harm.

Monitoring the Renal and Nephrovascular Effects of NSAID Therapy We suggest that patients with cardio-renal risk factors receive a complete nephrological assessment, including calculation of the estimated GFR, age-adjusted renal function, urinalysis, electrolyte and acid–base profiling (acidosis/ hyperkalemia), microalbuminuria, proteinuria (if any), concurrent anti-hypertensive therapy (anti-ANG II, anti-aldosterone treatment). Measurement of serum chloride is particularly useful [107]: at \ 100 mmol/l, Cl- predicts a setting of metabolic alkalosis (diuretics, hyperaldosteronism); at [105 mmol/l, it suggests a hyperchloremic metabolic acidosis (renal failure with normal anion gap). Failure of Cl- to increase in the presence of metabolic acidosis with low HCO3 - levels implicates an elevated anion gap acidosis, resulting from an unmeasured anion (ketones, lactate, alcohol metabolites, salicylate or other intoxications, sepsis). Both alkalosis and acidosis usually drive significant changes of serum K?, potentially relevant to treatment with NSAIDs, which tend to increase K? by interfering with prostacyclinmediated K? secretion in the distal tubule. If used in conjunction with an angiotensin-converting enzyme inhibitor (ACEi) or ANG II receptor antagonist in a diabetic patient, the risk of hyperkalemia is greatly increased.

Practical Indications

(1) NSAIDs have very modest effects in the healthy kidney and/or younger individuals and are usual ly well tolerated in subjects with normal renal function.

(2) Any patient with chronic renal dis ease should be warned against possible sideeffects of NSAIDs, both in terms of renal function and/or blood pressure control. Should a course of NSAIDs be deemed necessary, the follow ing measures should be taken:

i. Obtain a baseline measurement of renal function (i.e. estimated [e]GFR by Cockroft-Gault, CKD-EPI or MDRD equations) and serum K?.

ii. Withdraw any concurrent anti-hypertensive therapy with ACEi or ANG II receptor blockers (known to decrease eGFR in elderly patients with widespread atherosclerotic vascular lesions).

iii. Keep daily doses of the chosen NSAID to the lowest effective level, for no longer than 1 week to 10 days.

iv. Avoid dehydration or concurrent diuretic therapy, unless mandatory.

v. Monitor eGFR and serum K on weekly basis. Virtually all non-selective COX-1 and -2 inhibitors have the potential to induce or aggravate AKI; selective COX-2 inhibitors (rofecoxib, celecoxib) can also affect renal function, whereas NSAIDs with higher COX-2 selectivity (diclofenac, meloxicam) also have renal effects, however not statistically significant.

vi. Closely monitor individuals with increased risk of AKI due to underlying comorbidities (arterial hypertension, diabetes, heart failure, stroke).

vii. Withdrawal of NSAIDs is almost always followed by recovery of renal function, although not all cases of AKI are entirely reversible.

Tables 5 and 6 summarize the indications on the selection of the most adequate NSAID according to the CV, GI and renal risk (low vs. high).

PATIENT MANAGEMENT DURING NSAID THERAPY

The management of pain relies on a s quential pharmacologic approach. Following the core principles of patient-centered care [108], the treatment plan must be periodically revised based on the assessment of response (in terms of both efficacy and tolerability) and adherence, taking into consideration the possibility to switch to other options in case of inefficacy or intolerance.

When is it Appropriate to Re-evaluate the Patient Receiving NSAID Therapy and What Aspects Should Be Reevaluated?

In OA, an effective treatment improves both pain and physical function: as already stated, the same NSAID at different dosages exerts different effects and the minimum effective dose is defined in efficacy studies [21]. Therapy duration must be tailored to the patient profile [61] and the revision of the treatment plan must be periodic.

When revising the treatment plan, efficacy, tolerability, and adherence must be assessed.

A complete assessment should include the following: evaluation of pain through any of the available scales (VAS, NRS and WOM-

Key points

- NSAIDs and Arterial Pressure
  The pro-hypertensive effects of NSAIDs are believed to stem from three major mechanisms:
  (1) Na+ and Cl- retention and in creased antidiuretic hormone-mediated water reabsorption at the distal collecting duct
  (2) Blockade of the vasodilator effects of PGE2 and PGI2 on the kidney microcirculation
  (3) Unbalanced activity of the renin/ angiotensin/ aldosterone axis, nor mally regulated by local vascular and tubular eicosanoid biosynthesis.

Table 4 Risk factors in NSAID users requiring prophylaxis with proton pump inhibitors

Risk factors requiring prophylaxis with PPIs
History of ulcer complications, particularly bleeding
Age[65 years
Prior ulcer even without complications
NSAIDs/coxibs at higher doses or in combination with other gastrotoxic drugs or anti-coagulants (e.g. multiple NSAIDs/coxibs, steroids, SSRIs, warfarin)
ASA alone, even at low dosage in elderly patients, or combined with other drugs (e.g., NSAIDs/coxibs, steroids, anticoagulants, clopidogrel)
Ticlopidine or clopidogrel in high-risk patients
Acute NSAID/coxib use in patients taking chronically anti-coagulant or anti-platelet drug

PPIs proton pump inhibitors, NSAIDs non-steroidal anti-inflammatory drugs,coxibs COX-2-selective NSAIDs, Plus ASA acetylsalicylic acid, SSRIs selective serotonin reuptake inhibitors

Key points

- The management of pain relies on a squential pharmacologic approach. Following the core principles of patient-centered care, the treatment plan must be periodically revised based on the assessment of response (in terms of both efficacy and tolerability) and adherence, taking into consideration the possibility to switch to other options in case of inefficacy or intolerance.

AC), impact on the quality of life, pain tolerability, functional recovery and therapy duration. Factors that may help increasing compliance are dosage, regimens and formulations.

Practical Indications

Treatment response and adherence should be periodically re-evaluated, using scales to assess pain and function.

CONCLUSIONS

This narrative review provides practical indications for GPs and specialists managing patients with OA who suffer from chronic inflammatory pain. Selection of the appropriate therapy is hampered by the patients often being elderly and burdened with comorbidities and polypharmacy. Thus, both patient and drug characteristics (i.e. pharmacology, interactions and benefit/risk balance) must be carefully evaluated, keeping in mind that the same NSAID at different doses has different effects on pain and physical function. To summarize:

- During the first visit, the GP must investigate the origin, duration and component of pain, and collect in formation on possible risk factors for CV, GI and renal AEs, including comorbidities and concomitant therapies.
- If a non-pharmacological intervention is planned, the physiatrist comes into play, providing a person centered, holistic approach that accounts for the individual conditions globally.
- If the patient has to receive a pharmacological intervention, the selection of the most appropriate NSAID, of possible drugs to be used in combination or to be avoided, of the formulation and of ther apy duration must rely on both the patient profile and the drugs' pharmacological properties (i.e., COX isoform selectivity and potency and plasma half-life):
  – in OA patients with inflammatory pain, the use of paracetamol must be avoided as it is ineffective.
  – the dose to be administered is the minimum effective dose as determined by available studies.
  – in low-risk patients, therapy must be administered for at least 10 days to achieve analgesia and 3 weeks to achieve the full anti-inflammatory effect.
- *NSAID safety:* The main determinants of the risk of AEs are the individual baseline risk (in case of high risk, specific parame ters should be monitored during therapy) and the drug's safety profile. Possible drug–drug interac tions must be considered.

Table 5 Indications on the selection of the most adequate NSAID according to the cardiovascular and gastrointestinal risk, in patients with low renal risk

Low renal risk		
CV risk	GI risk	
	Low	High
Low	Diclofenac	Diclofenac + PPI
	Coxib	Coxib + PPI
	Ibuprofen	Ibuprofen + PPI [a]
	Naproxen	Naproxen + PPI
High	Naproxen	Any NSAID
	Diclofenac	
	Coxib	
	Ibuprofen	
High + LDA	Diclofenac [b]	Any NSAID
	Coxib	
	Ibuprofen	
	Naproxen	

In italics, compounds indicated based on the available randomized controlled trials. Underlined, compounds contraindicated based on the available randomized controlled trials
GI gastrointestina, PPI proton-pump inhibitor, CVcardiovascular,NSAID non-steroidal anti-inflammatory drug, LDA low-dose aspirin
[a] Up to 1200 mg per day
[b] Use only if NSAID therapy is strictly necessary, and for a limited period of time

Table 6 Indications on the selection of the most adequate NSAID according to the cardiovascular and gastrointestinal risk, in patients with high renal risk

High renal risk		
CV risk	GI risk	
	Low	High
Low	Diclofenac/other selective COX 2 inhibitors at the lowest effective level, for no longer than 7 to 10 days	Any NSAID
High	Any NSAID	Any NSAID
High + LDA	Any NSAID	Any NSAID

In italics, compounds indicated based on the available randomized controlled trials. Underlined, compounds contraindicated based on the available randomized controlled trials
GI gastrointestinal, COX-2 cyclooxygenase,NSAIDnon-steroidal anti-inflammatory drug, CV cardiovascular,LDA low-dose aspirin

Key points

- Selection of the appropriate therapy is hampered by the patients often being elderly and burdened with comorbidities and polypharmacy. Thus, both patient and drug characteristics (i.e. pharmacology, interactions and benefit/risk balance) must be carefully evaluated, keeping in mind that the same NSAID at different doses has different effects on pain and physical function.
  – to limit the CV risk, the only indication is to adhere to the recommended dosages and duration and, possibly, undergo cycles of therapy with periodical interruptions. The use of ASA limits the choice of NSAIDs.
  – NSAID-induced GI damage can be significantly reduced through the administration of PPIs in the presence of particular risk factors.
  – NSAIDs have very modest effects in the healthy kidney and/or younger individuals and are usually well tolerated in subjects with normal renal function. Adjust treatment to the individual needs, keeping it as short as possible, while monitoring key renal function parameters in elderly patients or subjects with known renal disease, reduced renal function, or high-risk conditions, including diabetic nephropathy or cardio-renal syndromes.
- *Periodically re-evaluate treatment response and adherence*, using scales to assess pain and function.

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■ **Wynand Steenkamp, Pududu Archie Rachuene, Roopam Dey, Nkosiphendule Lindani Mzayiya, and Brian Emmanuel Ramasuvha**

The correlation between clinical and radiological severity of osteoarthritis of the knee

ABSTRACT: Introduction: Primary osteoarthritis (OA) is a common cause of knee pain. Appropriate management of knee OA is based on clinical and radiological findings. Pain, deformity, and functional impairments are major clinical factors considered along with radiological findings when making management decisions. Differences in management strategies might exist due to clinical and radiological factors. This study aims at finding possible associations between clinical and radiological observations. Methods: A prospective cross-sectional study of 52 patients with primary osteoarthritis of the knee managed conservatively at a tertiary hospital arthroplasty clinic was conducted for three months. English speaking patients with primary OA were identified and included in this study. Pain and functional impairment were assessed using Wong-Baker Faces pain scale, The Knee Society Score (KSS), and Western Ontario and McMaster Osteoarthritis Index (WOMAC). The Body Mass Index (BMI) of all participants was measured. Standard two views plain radiographs were used for radiographic grading of the OA. Anonymized radiographs were presented to two senior consultant orthopaedic surgeons who graded the OA using Kellgren and Lawrence (KL) and Ahlbäck classification systems. The severity of the functional impairment and pain score was then compared to the radiological grading. Results: The average age of our participants was 63 ± 9 years. Their average BMI was 34.9 ± 8.4 kg/m2 , median self-reported pain, total WOMAC, and pain WOMAC scores were 8, 60, and 13, respectively. We observed no significant correlation between BMI and pain scores. Inter-rater reliability for KL and Ahlbäck grading was strong. There was no significant correlation between WOMAC scores and the radiological grades.

Conclusion: There was no correlation between pain and functional scores, patient factors and radiological severity of OA of the knee.

Keywords: Osteoarthritis, Knee, Functional impairment, Radiologic grading.

INTRODUCTION

Osteoarthritis (OA) is the most common joint pathology seen worldwide and is the leading cause of disability in the United States [1]. It affects over 40 million people in Europe [2]. Even though the exact cause is still unclear, numerous contributing factors have been identified. The common final pathway is characterized by progressive cartilage matrix degradation to which an ineffectual attempt at repair is made. This leads to cartilage failure causing joint pain, loss of joint function and eventually deformity [3]. Patients commonly present with multiple joint involvements, with the knee being affected in 6% of the adult population [4]. Literature suggests that up to 19% of the rural community in Africa have symptomatic OA of the knee, and a population-based study from a South African rural setting reported a knee osteoarthritis prevalence of 33.1% among adults aged over 35 years [5, 6].

Diagnosis of osteoarthritis of the knee is based on clinical and radiological findings. No universally accepted guidelines or diagnostic criteria h exists [3]. The typical clinical features of OA of the knee include knee pain, decreased range of motion, crepitations, bony tenderness, knee bony enlargement and instability [7]. Knee pain is the most common symptom, and its cause is multifactorial, with both nociceptive as well as neuropathic mechanisms contributing towards it. The cartilage damage, subchondral bone pathology, periosteum, synovium as well as soft tissue have all been thought to contribute to the pain [8, 9].

Grading the clinical severity of knee OA needs to consider multiple factors. Acute pain can be graded using visual analogue or numeric scores. But chronic pain and functional impairment require a more comprehensive grading system. The Knee Society Score (KSS) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) provide a holistic understanding of the impact and severity of the OA in the knee [10, 11].

Despite recent advances in imaging modalities, plain radiographs remain the gold standard imaging modality in diagnosing OA of the knee and ruling out other causes of knee pain [7]. The X-ray views required to assess all three compartments of the knee include weight-bearing anteroposterior and lateral views, Rosenberg view, and the skyline view. Although X-rays can readily be used to detect bony changes secondary to osteoarthritis, the amount of soft tissue involvement remains unclear. Measuring the joint space on X-rays is used as an indirect method to assess the joint cartilage. Unfortunately, the joint space consists of cartilage and includes other soft tissue structures such as the menisci, ligaments, and synovium. Osteophyte formation, joint surface deformation, subchondral sclerosis and cysts make up the typical X-ray features of osteoarthritis [12].

As early as 1957, Kellgren and Lawrence (KL) described a radiographic classification system for osteoarthritis. It considers four features: 1. Joint space narrowing (JSN), 2. osteophyte formation on the joint margins or tibial spines, 3. subchondral

Table 1. Summary of related published articles and their findings.

Author	Title	Relevant results
Szebenyi et al. [16]	Associations between pain, functional, and radiographic features in osteoarthritis of the knee	• Higher levels of pain reported if all compartments of the knee involved • Subchondral sclerosis linked to pain, rather than global radiological grading
Polat et al. [8]	Is there a possible neuropathic pain component in knee osteoarthritis	• Radiological grading severity linked to age rather than degree of pain reported
Kocak et al. [17]	Associations between radiographic changes and function, pain, range of motion, muscle strength and knee function score in patients with osteoarthritis of the knee	• KL grade III and IV correlated to more severe clinical features
Talic-Tanovi et al. [19]	Comparison of clinical and radiological parameters at knee osteoarthritis	• Females had higher levels of OA of knee • No significant correlation between clinical and radiological severity of OA of knee
Zheng et al. [21]	Body mass index and risks of knee osteoarthritis: systematic review and meta-analysis of prospective studies	• BMI is an independent predictor of OA of the knee
Alahmari et al. [23]	Mediating role of body mass index in knee osteoarthritis	• Higher BMI levels correlated to more severe levels of pain reported

Key points

- Diagnosis of osteoarthritis of the knee is based on clinical and radiological findings. No universally accepted guidelines or diagnostic criteria h exists. The typical clinical features of OA of the knee include-
  - -Knee pain
  - -Decreased range of motion
  - -Crepitations,
  - -Bony tenderness
  - -Knee bony enlargement
  - -Instability

sclerosis, and 4. bone-end deformation. Although it has some limitations, it is still the most commonly used grading system [13]. In 1968 Ahlbäck investigated the radiological appearance of the knee in osteoarthrosis, and subsequently published the Ahlbäck classification in 1980 [14, 15]. In contrast to the KL classification, which emphasizes the formation of osteophytes, the Ahlbäck classification focuses more on the amount of joint
space narrowing and bone attrition.

A review of the literature showed inconsistent results between the severity of clinical features compared to radiological gradings (Table 1). Szebenyi et al. reported that patients were more likely to have pain if radiological changes were seen in the tibiofemoral compartments and the patellofemoral compartments. They also found that subchondral sclerosis was linked to pain rather than a global grading as by KL [16]. Polat et al. considered that some patients with knee OA had a neuropathic pain component that contributed to the overall joint pain. The authors also found that the radiologic grading correlated to the patients' age than the reported degree of pain [8]. Contrary to this, Kocak et al. found that patients with KL grades III and IV radiological features had more pain, lower muscle strength, range of motion, and functional scores than patients with KL I and II [17].

Knee OA patients in sub-Saharan Africa often belong to the underprivileged sections of society. Often, they are incapable of affording a thorough clinical examination, and the clinician has to decide depending on the only available information, which can either be radiological or clinical. There is no evidence on the association of clinical and radiological observations in the sub-Saharan population Understanding such associations will assist clinicians in managing knee OA patients. Therefore, the primary aim of this study was to compare radiographic findings
to pain severity and functional impairments in patients with osteoarthritis of the knee joint. The secondary aim was to assess if Body Mass Index (BMI) contributed to the severity of either clinical or radiological parameters.

Materials and methods

A prospective cross-sectional study was conducted from April 2021 until June 2021 after obtaining institutional ethics clearance and hospital gatekeeper permission. A total of 52 English speaking patients with primary knee OA who were treated conservatively and followed up at a tertiary academic hospital arthroplasty clinic were included in this study.

The average age of the cohort was 63 ± 9

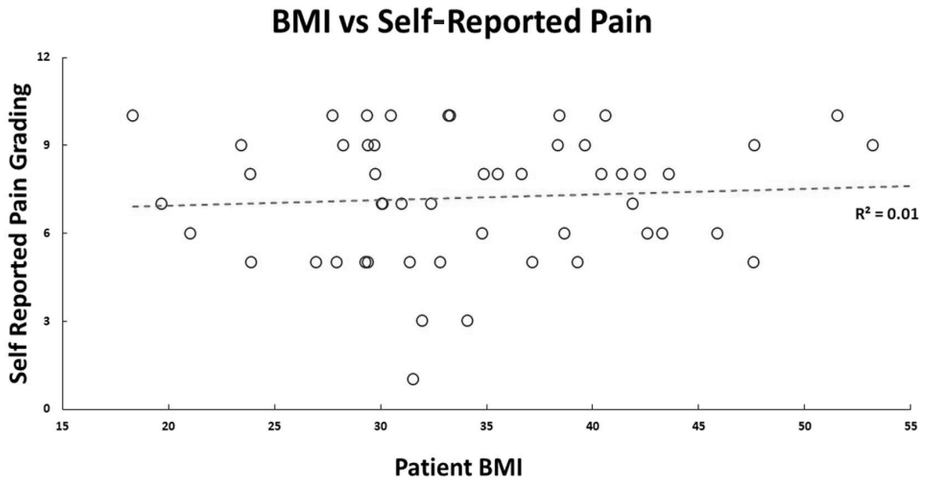

Figure 1. Patient self-reported pain score plotted against their BMI, and their linear relationship is shown by the red dashed trend line.

years. Patients with secondary knee arthritis were not included in the study. Prior to participating in this study, participants gave their informed consent. They were then asked to fill out a standard questionnaire with their demographic information (age, sex, weight, and height). The subjects also filled in self-reported pain grading information (numeric pain rating scale and Wong-Baker FACES pain rating scale) and functional assessment information (Knee Society Score and Western Ontario and McMaster Osteoarthritis Index).

As part of our institution's standard of care for patients with OA of the knee, plain knee X-rays are repeated and reviewed at 3 monthly intervals to evaluate the progression of the disease. The principal author provided reviewers with anonymized X-rays consisting of an anteroposterior and a lateral view. To improve the validity and reliability of this analysis, 2 orthopaedic consultant reviewers were simultaneously tasked to assess the X-rays independent of each other and grade them using standard KL as well as Ahlbäck classification systems.

Data was compiled by the principal investigator and assessed only after all the data had been collected. The functional impairment and pain severity were compared to the radiological grading to determine if any association existed. Secondly, the data was assessed to determine whether there was any correlation between the patients' age or BMI compared to clinical and radiological severity.

All statistical analyses were performed in IBM SPSS v.27 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as average (standard deviation) or median (max; min) depending on the distribution. Inter-rater reliability was calculated using the intra-class correlation coefficient (ICC) with a two-way mixed model absolute agreement. ICC values were presented as (average measures ICC; 95% confidence interval). Kendall's tau correlation coefficient was calculated between WOMAC scores and radiographic gradings. Correlation coefficients were also calculated between pain scores (self-reported and WOMAC) and patient BMI. The cut-off for statistical significance for all the tests was set as $p < 0.05$.

Results

Our cohort had 92% female participants. Their average weight, height, and BMI were 91.8 (±21.3) kg, 1.6 (±0.1) m, and 34.9 (±8.4) kg/m2 , respectively. There were 69.2% obese participants, 19.2% overweight participants, 11.2% had healthy BMI. The median self-reported pain grading was 8 (1; 10), and

Key points

- Knee pain is the most common symptom, and its cause is multifactorial, with both nociceptive as well as neuropathic mechanisms contributing towards it. The cartilage damage, subchondral bone pathology, periosteum, synovium as well as soft issue have all been thought to contribute to the pain.

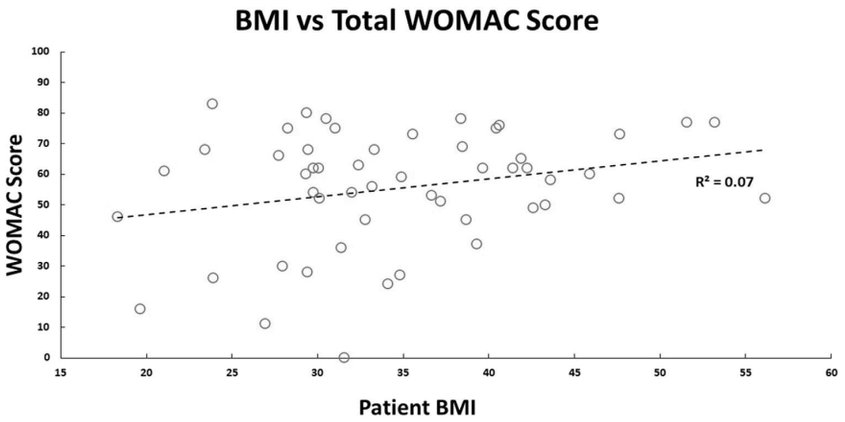

Figure 2. Patient WOMAC score plotted against their BMI, and their linear relationship is shown by the black dashed trend line.

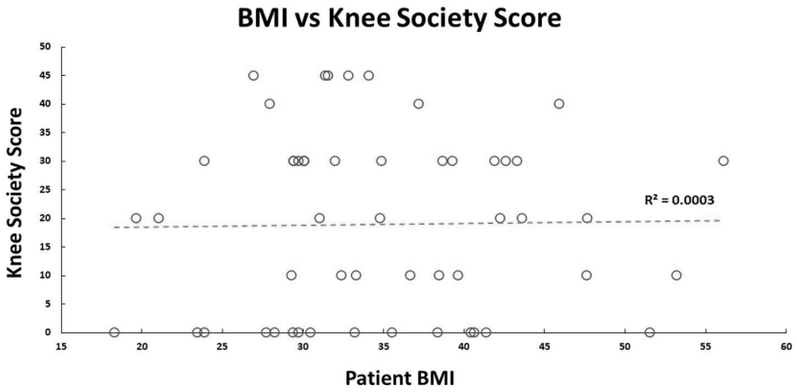

Figure 3. Patient Knee Society score plotted against their BMI, and their linear relationship is shown by the green dashed trend line.

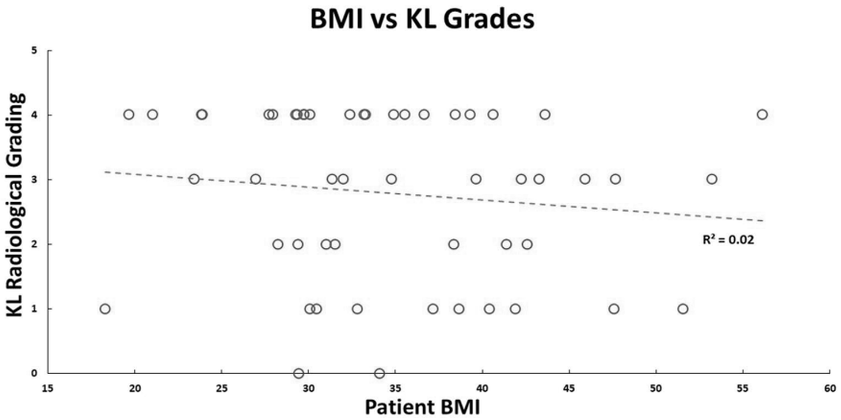

Figure 4. Patient Kellgren and Lawrence radiological grading plotted against their BMI, and their linear relationship is shown by the blue dashed line.

Knee Society Score was 20 (0; 40). Medians for WOMAC scores were – total: 60 (0; 83); pain: 13 (0; 17); stiffness: 5 (0; 8); functional: 42 (0; 62). There was no significant correlation between pain (self-reported, KSS, and WOMAC) with participant's BMI (Figures 1 and 2) and age. No walking aid was used by 50% of our participants; 25% of them used a single crutch, followed by 15.4% who used double crutches. The rest of them used a walking stick (7.7%) and a walker (1.9%).

There was strong inter-rater reliability ($p < 0.001$) for KL (ICC: 0.82; 95% CI: 0.68–0.89) and Ahlbäck (ICC: 0.87; 95% CI: 0.77–0.92) radiographic classifications. The median KL grade was 3 (0; 4), and Ahlbäck grade was 3 (1; 5). The radiological scores had a statistically significant ($p < 0.01$) medium correlation (0.73) with each other (Figures 3–5). There was no significant correlation between the radiological gradings with WOMAC scores and KSS (Figure 2). The Knee Society Score had a statistically significant ($p < 0.01$) negative correlation with WOMAC scores, ranging from 0.41 to 0.61 (Figure 6).

Discussion

Deciding on a management plan for patients with OA of the knee can be complex. Treatment needs to be individualized per patient, and the main aim of treatment should be to relieve pain

Key points

- Grading the clinical severity of knee OA needs to consider multiple factors. Acute pain can be graded using visual analogue or numeric scores. But chronic pain and functional impairment require a more comprehensive grading system.
- The Knee Society Score (KSS) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) provide a holistic understanding of the impact and severity of the OA in the knee.

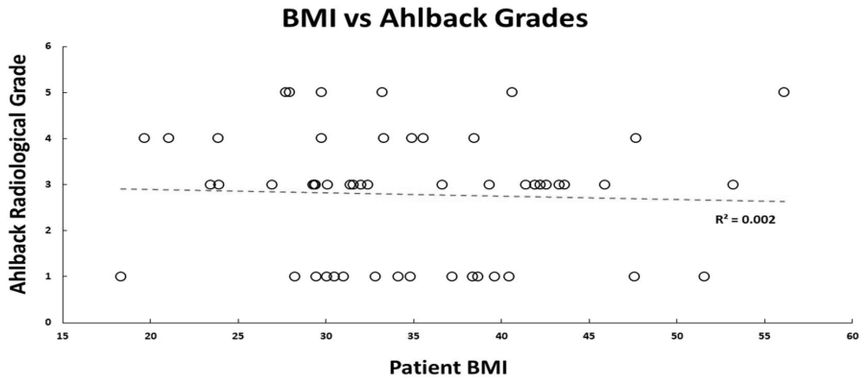

Figure 5. Patient Ahlbäck radiological grading plotted against their BMI, and their linear relationship is shown by the blue dashed line.

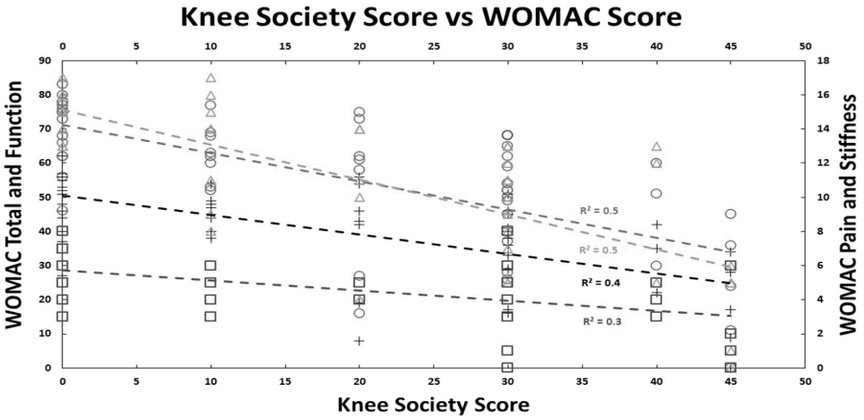

Figure 6. Patient WOMAC score components plotted against their Knee Society Scores (KSS). Total WOMAC score is represented by the blue color, the Pain component is represented by the orange color, the Functional component is represented by the black color, and the Stiffness component is represented by the purple color. Each component s linear relationship with KSS is represented by the dashed in their respective colors.

Key points

- Despite recent advances in imaging modalities, plain radiographs remain the gold standard imaging modality in diagnosing OA of the knee and ruling out other causes of knee pain.
- The X-ray views required to assess all three compartments of the knee include weight-bearing anteroposterior and lateral views, Rosenberg view, and the skyline view.
- Although X-rays can readily be used to detect bony changes secondary to osteoarthritis, the amount of soft tissue involvement remains unclear. Measuring the joint space on X-rays is used as an indirect method to assess the joint cartilage.

and optimize function [18]. Treatment usually consists of conservative management initially, with surgery as an option for those who do not respond. Both clinical as well as radiological parameters, should be considered when such decisions are made. For this reason, it is essential to understand the relationship between the two.

Our study did, however, have some limitations. Firstly, a single interview was conducted with the participants, and we did not follow them up to assess if the progression of radiological severity affected their clinical severity. Secondly, the study was conducted at a tertiary hospital. Therefore, these patients had already failed treatment at primary or secondary care. This might influence the severity of symptoms reported by participants.

In our study, the vast majority (92%) of participants were female. This correlates to previous studies that showed a higher incidence of OA in females [14, 19]. Western Ontario and McMaster Osteoarthritis Index (WOMAC) score consist of three subsections: Pain, stiffness and function. It provides a global picture of the symptoms and their impact caused by OA of the knee. The KSS is a functional assessment of the impact of pain caused by OA of the knee. Our study found no correlation between either the WOMAC score or KSS score when compared to the severity of the radiographs as classified by either KL or Ahlbäck (Figure 7). This is in keeping with the results found by Talic-Tanovi et al. and Szebenyi et al. However, we did not, find a correlation between subchondral sclerosis and pain as found by Szebenyi et al. [8, 16, 19].

This is in contrast to Kocak et al., who found that higher patients with higher-grade radiological gradings suffer from more severe clinical features [17].

This could be that the exact origin of the pain and sequelae thereof is still poorly understood. However, it suggests that OA is not just purely a degenerative condition of the cartilage but does involve an inflammatory as well as soft tissue component. This supports the study by Roemer et al. that suggested that OA is not just a disease of the cartilage but involves the whole joint as well as other soft tissue that eventually leads to joint failure [20].

A systematic review and meta-analysis by Zheng et al. showed that body mass index (BMI) was an independent predictor for OA of the knee [21]. It has also been shown that

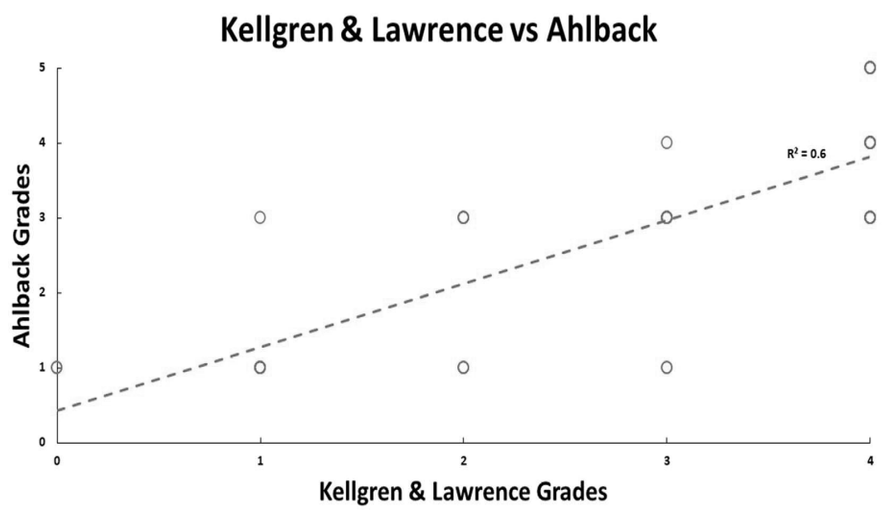

Figure 7. Patient Ahlbäck radiological grades plotted against Kellgren and Lawrence s radiological grades, and their linear relationship is shown by the blue dashed line.

Key points

- The following factors make-up the typical X-ray features of osteoarthritis-
  - -Osteophyte formation
  - -Joint surface deformation
  - -Subchondral sclerosis
  - -Cysts

obesity is associated with both incidences as well as the progression of OA [22]. The body mass index of participants in our study ranged between 26.5 and 43.3, with a median score of 34.9. No correlation between the BMI and clinical or radiological severity was observed. This contrasts with previous studies that showed that a higher BMI correlates with more severe pain in patients with OA of the knee [23]. The reason for this could be that our median BMI was 34.9, thus the majority of our patients being obese or overweight already.

CONCLUSIONS

The discordance between clinical and radiological features of OA of the knee found in our study is in keeping with multiple previous studies. A thorough clinical evaluation of these patients is essential to determine the severity of the condition and decide on the appropriate management. Further studies are needed to identify the exact origin of the pain. Although X-rays still form part of the complete workup of patients with suspected OA of the knee, one needs to consider its shortcomings to grade the severity. Measuring the joint space as an indirect indicator of the cartilage quality is an easy and readily available technique, but it cannot be used in isolation to determine management. The gold standard imaging modality is yet to be determined, and further studies are needed.

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