

Recommendation

Evidence-Based Recommendations for the Management of Knee Osteoarthritis: A Consensus Report of the Turkish League Against Rheumatism

Diz Osteoartrit Tedavisinde Kanıta Dayalı Öneriler: Türkiye Romatizma Araştırma ve Savaş Derneği Uzlaş Raporu

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Objectives: Knee osteoarthritis (OA) is a common disease which causes pain, disability and great socioeconomic burden as a result. Turkish League Against Rheumatism (TLAR) initiated a project to prepare national, "evidence-based recommendations for the management of knee osteoarthritis" supported by expert-opinion in order to assist the physicians who are interested in knee OA in their daily clinical practice.

Materials and methods: The expert committee was composed of 25 academicians, 23 of whom were physical medicine and rehabilitation (PM&R) specialists (three also had rheumatology subspecialty) and two were orthopedic surgeons. At the first meeting, the previous guidelines were discussed, and 2008 Osteoarthritis Research Society International (OARSI) recommendations were decided to be taken as the fundamental template for national recommendations. Databases of the Pubmed, Embase, Cochrane, and Turkish Medical Index were used to search the literature, and this was carried out for the period between 2009-2010 for international publications since studies up to 2009 were present in the 2010 OARSI update. No limit was applied for searching of national publications. The selected relevant publications were graded according to evidence level and quality, and were sent to the members who were then asked to suggest propositions according to their experiences, knowledge, and review of the literature. After amalgamation and editing of new proposals, Delphi rounds were started. After five Delphi rounds, the propositions on which the members were in consensus, were discussed with regard to evidence and the "strength of recommendation" was determined by measuring on visual analog scale (VAS) for each proposal at the final meeting.

Results: Nineteen propositions (one for general principles, nine for non-pharmacologic treatments, seven for pharmacologic treatments, and two for surgical treatments) were accepted as the "TLAR Evidence-Based Recommendations for the Management of Knee OA" in consensus as a result of Delphi rounds.

Conclusion: Evidence-based recommendations for the management of knee OA were developed by TLAR for the first time in our country. The recommendations should be updated regularly according to new evidence and insights. It is expected that physicians who are interested in knee OA will benefit greatly from this report in their daily clinical practice.

Key words: Knee osteoarthritis; TLAR; treatment guideline.

Amaç: Diz osteoartriti (OA) sık görülen ve neden olduğu ağrı ve sakatlık sonucunda sosyoekonomik yük bindiren bir hastalıktır. Türkiye Romatizma Araştırma ve Savaş Derneği (TRASD) OA tedavisi ile uğraşan hekimlere günlük klinik uygulamalarında yardımcı olmak amacıyla, uzman görüşleri ile desteklenmiş, ulusal "diz osteoartrit tedavisinde kanıta dayalı önerileri" hazırlamak için bir proje başlatmıştır.

Gereç ve yöntemler: Uzmanlar komitesi 23'ü fiziksel tıp rehabilitasyon (FTR) uzmanı (üçü ayrıca romatoloji yan dal uzmanı) ikisi ise ortopedi ve travmatoloji uzmanı olan 25 akademisyenden oluşturulmuştur. İlk toplantıda konu ile ilgili önceden yayınlanmış rehberler üzerinde tartışılmış ve 2008 Osteoarthritis Research Society International (OARSI) önerilerinin ulusal öneriler için temel şablon olarak kullanılmasına karar verilmiştir. Literatür taraması için Pubmed, Embase, Cochrane ve Türk Tıp Dizini veritabanları kullanılmış olup, uluslararası taramalar için, 2009 yılına kadar yayınlanmış çalışmaların 2010 OARSI güncellemesinde yer almasından dolayı, 2009-2010 yıllarını kapsayacak bir süre kısıtlaması yapılmıştır. Ulusal yayınların taranması için tarih sınırlaması yapılmamıştır. Konuyla ilgili çalışmalar arasından seçilen makaleler kanıt düzeyi ve kalite açısından derecelendirilmiş, uzmanlar kurulu üyelerine gönderilerek kendilerinden mevcut kanıtlar ve kendi bilgi ve deneyimleri ışığında tedavi önerileri hazırlamaları istenmiştir. Hazırlanan öneriler bir araya getirilmiş, düzeltmeler yapılmış, sonrasında Delphi turları başlatılmıştır. Beş Delphi turu sonunda, üzerinde görüş birliği sağlanan öneriler son toplantıda kanıtlar ışığında tartışılmış ve vizüel analog skala (VAS) üzerinde değerlendirilerek her bir öneri için "öneri gücü" belirlenmiştir.

Bulgular: Delphi turları sonucunda, üzerinde görüş birliği sağlanmış olan 19 öneri (biri genel prensip, dokuz nonfarmakolojik, yedisi farmakolojik ve ikisi cerrahi tedaviler ile ilgili olmak üzere) "TRASD Diz Osteoartriti Kanıta Dayalı Tedavi Önerileri" olarak kabul edilmiştir.

Sonuç: TRASD tarafından, ülkemizde diz OA'sı ile ilgili ilk kanıta-dayalı tedavi önerileri oluşturulmuştur. Bu önerilerin yeni kanıtlar ve görüşler ışığında düzenli olarak güncellenmesi gerekmektedir. Bu önerilerin, diz OA'sı ile ilgilenen hekimlerin günlük pratiklerine katkısı olacağı beklenmektedir.

Anahtar sözcükler: Diz osteoartriti; TRASD; tedavi rehberi.

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Osteoarthritis (OA) is a degenerative joint disease which increases in frequency with age. Pain, disability, and deterioration in quality of life are the main consequences of the disease. It might be accepted as an organ disease since nearly all of the periarticular tissues are involved, even though the main injury is in the cartilage and subchondral bone. Osteoarthritis may be seen in any joint. Involvement of the spine or weight-bearing joints such as the hip and knee may result in more disabling conditions than other parts of the body. The prevalence of symptomatic knee OA was reported as 14.8% in our country and was more common in females.^[1] Bilateral involvement is frequent, and radiologic knee OA is estimated to be more common. Although many predisposing factors, such as genetic, metabolic, and mechanic disturbances, were blamed, the exact etiopathogenesis of knee OA has yet to be defined. Thus, an absolute cure for OA is not available. A symptomatic approach is widely used along with a variety of treatment options. Several national and international institutions, such as the European League Against Rheumatism (EULAR) and OARSI, have developed management guidelines for OA to assist physicians and patients.^[2-5] These guidelines were prepared by evaluating the present treatment options in light of scientific evidence as well as expert opinions. It is anticipated that these guidelines will be modified or adapted and periodically updated for national and regional use, with a perspective toward the social requirements and legal rules of the community. In this context, the Turkish League Against Rheumatism (TLAR) has initiated a project to provide recommendations for the management of several rheumatic diseases.

The objective of this study is to prepare national, evidence-based recommendations in conjunction with expert consensus for the management of knee OA, a disease which has disabling and socioeconomic consequences. These recommendations are intended to provide assistance and updated evidence to physicians who deal with patients with knee OA.

MATERIALS AND METHODS

In April 2010, TLAR made a general announcement to members by e-mail to determine which experts desired to participate in the development of recommendations for the management of knee OA and requested for those who were interested to fill out a form consisting of their experience, knowledge, skills, and scientific publications in the field of OA. These forms were then analyzed and an "Expert Committee" was appointed.

Two orthopedic surgeons who have experience on knee OA were also invited to be on the committee. The committee was composed of 25 physicians with 23 physical medicine and rehabilitation (PM&R) specialists (three had rheumatology subspeciality) and two orthopedic surgeons. A project coordinator and two assistants were assigned to coordinate, search, and review the literature as well as write the final manuscript. It was decided that they should not be involved in the process of the development of the recommendations. Before the first meeting, coordinators sent existing guidelines and recommendations concerning the management of knee OA to the committee members. At the meeting, the committee discussed the previous recommendations of 2003 European League Against Rheumatism (EULAR), the National Institute for Health and Clinical Excellence (NICE), the American Academy of Orthopedic Surgeons (AAOS), 2008 OARSI recommendations and 2010 OARSI update.^[2-6] The committee agreed to select the "2008 OARSI Recommendations for the Management of Osteoarthritis of the Hip and Knee" as a template for our preparation due to its most recent update, comprehensive aspects, and international scope. The committee decided to make necessary modifications with regard to new scientific evidence and their knowledge and experience as well as our national conditions. Experts discussed the methodology related to the literature search and the process for developing recommendations. General principles, non-pharmacologic treatments, pharmacologic treatments, and surgical treatments were chosen as the main topics for the planned recommendations. Then several sub-topics under the headings of the main topics were also defined. It was decided that the acceptance level for the 2008 OARSI recommendations would be determined by committee members. In this context, it was planned that the original version of this report would be sent to committee members for assesment on a 0-100 mm visual analogue scale (VAS), and afterwards, the mean level of acceptance for each proposition would be calculated statistically.

A systematic literature search was performed for only the period between 2009 and 2010 for international publications, since studies up to January 1st, 2009 were present in the 2010 OARSI update. No limit was applied for national literature since pertinent articles could not be found in this way. The databases of Pubmed, Embase, Cochrane, and the Turkish Medical Index were used to search the literature. Reports concerning OA of joints other than the knee

and those which were not relevant to management were left out of the evaluation. Publications relevant to the management of knee OA were ranked according to the quality of publication and evidence level of the study. Evidence level evaluation was performed according to Table 1.^[7] Meta-analyses (MA) and systematic reviews (SR) were graded by using the Oxman-Guyatt index while randomized controlled trials (RCTs) were graded according to the Jadad scale.^[8,9] If an MA or RCT existed for any title, any other study with a lower grade was ignored. The report with the highest quality score was selected for evaluation if more than one on the same subject were present. Studies which were not randomized were excluded from quality assessment. Concerning the efficiency and side effects of any treatment regimen, the effect size (small being up to 0.4; moderate 0.4-0.8; and large if higher than 0.8), number needed to treat (NNT), relative risk (RR) and odds ratio (OR) were recorded if available.^[10,11]

The publications which were evaluated in the context of the above rules were sent to the experts who were asked to suggest 23 propositions according to their experiences, knowledge, and review of literature by taking into account the 2008 OARSI recommendations as the fundamental template. The propositions should cover all the topics defined at the first meeting. A total of 477 propositions covering various categories were sent back by the experts (Table 2). The coordinators eliminated and amalgamated similar or overlapping propositions and sent them back to the members for any necessary revisions. Delphi rounds were then started with 114 propositions. In the first of the Delphi round, the experts were asked to choose 20 propositions from all of the sub-topics. A proposition was accepted if approved by >60% of the experts and was rejected if approved by <20%. Any proposition with an approval of between 20-60% was included in the next Delphi

round. After five rounds of Delphi exercises, a total of 19 propositions were selected. These propositions were written with relevant evidence from recent literature and sent back to the experts for reevaluation at the final meeting.

At the final meeting, the experts created the final version of the manuscript with a consensus regarding further additions or removals and minor rewording. Any difference made in any proposition was voted on, and a consensus was reached. At the same meeting, each expert was asked to determine the level of acceptance for each of the 19 propositions on a 0-100 mm VAS by taking into consideration all evidence and discussions. The mean and 95% confidence interval (CI) of the acceptance level for each proposition was defined as the strength of recommendation (SOR).

RESULTS

The expert committee evaluated the 2008 OARSI recommendations on the VAS. As a result, the minimum and maximum levels for accepting each of the 25 propositions were found to be between 51% (95% CI 40-62) and 97% (95% CI 94-100), respectively.

At the end of five Delphi rounds, 19 propositions (one for general principles, nine for non-pharmacologic treatments, seven for pharmacologic treatments, and two for surgical treatments) were suggested as TLAR evidence-based recommendations for the management of knee OA (Table 3). The level of evidence (LOE), consensus level, and strength of recommendation for these propositions are shown in Table 4.

Table 1. Level of evidence for trials

LOE	Explanation
Ia	Metaanalysis of randomized controlled trials
Ib	At least one randomized controlled trial
IIa	At least one well-designed controlled study, but without randomisation
IIb	At least one well-designed quasi-experimental study
III	At least one non-experimental descriptive study (comparative, correlation or case-controlled study)
IV	Expert committee reports, opinions and/or experience of respected authorities

LOE: Level of evidence.

Table 2. Initial propositions before the modifications made by the coordinators

Category	Suggested propositions (n)
General principles	33
Nonpharmacologic management	
Education	29
Daily living activities	44
Exercises	28
Physical therapy applications	57
Assistive & adaptive devices	55
Balneotherapy	25
Complementary & alternative medicine	14
Pharmacologic management	
Oral and topical drugs	99
Intraarticular injections	36
Surgical management	57
<i>Total</i>	477

Table 3. TLAR evidence-based recommendations for management of knee OA

1. The main goal in the treatment of knee OA should be directed toward controlling pain, preserving and improving the function of joints, providing functional independency, and increasing the quality of life. In order to reach these goals, management of knee OA should contain non-pharmacologic, pharmacologic, and, when necessary, surgical approaches. Treatment should be tailored for each patient individually.
2. Educational programs about the symptoms of the disease, composition, and treatment objectives, designed for individuals and patient groups, may increase the adherence of patients to the therapy. These educational programs should contain lifestyle alterations, joint protection techniques, and diet and exercise programs which would provide weight control.
3. Patients with knee OA should be informed and encouraged to use their joints in a manner that allows the least amount of loading on their joints during their occupational, sports, and daily living activities. They should be educated to make this a principle part of their daily lives. The conditions at their home and office should be designed according to their disease. Patients should be advised to avoid climbing stairs, sitting cross-legged, squatting, kneeling during “namaz (an Islamic prayer)” or doing any other activity which would cause loading and enforcement of knee flexion. Using elevators, sitting without knee flexion during “namaz”, and using a Western-style toilet should be advised instead.
4. Age, comorbid diseases, and degree of OA should be taken into consideration when choosing an appropriate exercise program for each individual patient. Patients should be encouraged to do range-of-motion, stretching, isometric, isotonic, balance, proprioception, and aerobic exercises. Aquatic exercises can be planned in concert with the preferences of the patient and physician. The exercise programs should be taught to patients in a manner that they can clearly understand and be able to do on their own. Initially, they should be under supervision, but when the patients are able to do them by themselves, home programs should be started.
5. Physical medicine and rehabilitation specialists may advise the use of an appropriate walking stick, walker, or similar walking aid after the evaluation of the patients. These devices may decrease the patients’ pain levels; therefore, they should be educated regarding the correct use of these devices.
6. In knee OA patients with mild to moderate joint instability, the use of appropriate orthoses may decrease the risk of falling and may help to restore the stability. Each patient should be advised to choose convenient, comfortable, soft-soled shoes. The use of sole plates may help ambulation by decreasing pain in patients with knee OA. The application of a laterally-wedged insole in the shoes may have a symptomatic benefit in patients with medial tibiofemoral OA.
7. Electrotherapeutic agents such as TENS, interferential currents, and diadynamic currents may have beneficial effects on pain, joint function, and quality of life. Superficial and deep heat (ultrasound, short wave diathermy) applications may provide benefits for patients with knee OA who have no active synovitis. Cold application should be advised in the case of synovitis.
8. Neuromuscular electrical stimulation is one of the physical treatment modalities- considered not only for muscle strengthening but also as an alternative modality for alleviating the pain and functions of patients who are not able to take part in exercise programs.
9. If there is no contraindication, balneotherapy may be recommended for at least two weeks of treatment because of its thermal and non-thermal effects. Patients who are advised to have balneotherapy should be informed about the thermal and mineral aspects of the water of the center that they plan to attend. In addition to this treatment, peloidotherapy may be advised. Balneotherapy may be combined with other physical treatment modalities and exercises by a PM&R specialist.
10. Complementary treatment options should not be used instead of standard pharmacologic and non-pharmacologic treatments. But if it would be, it should only be used as an additional treatment. Both the beneficial and adverse effects of complementary treatments should be followed carefully.
11. Acetaminophen (maximum 3 g/day) as an initial treatment may have a mild analgesic effect in patients with knee OA who have a mild/moderate degree of pain. Alternative treatment options should be considered in case of inadequate response or the presence of severe pain and/or inflammation.
12. Nonselective and selective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors should be used at their lowest efficacious doses for conditions in which there is moderate to severe pain or synovitis and for situations in which paracetamol is insufficient. Concomitant use of two NSAIDs should be avoided. Gastroprotective agents should be combined with NSAIDs in patients with gastrointestinal complaints. Precaution should be taken with the use of NSAIDs if hypertension exists or renal or hepatic dysfunction are present.
13. Topical NSAIDs or capsaicin can be used in combination with other analgesic and/or anti-inflammatory drugs, or they can be used on their own if patients are unable to take other drugs.
14. Intraarticular glucocorticoid injection, not more than three times a year, can be applied in cases of symptomatic knee OA with signs of inflammation which are unresponsive to other treatment options.
15. Hyaluronic acid injections may be beneficial for patients with mild and moderate OA who are not overweight, have no instability, and are unresponsive to non-pharmacologic and pharmacologic treatment modalities.
16. Glucosamines and/or chondroitin sulfate may provide symptomatic benefits for patients with knee OA.
17. Administration of weak opioids or narcotic analgesics can be considered for patients with knee OA who are resistant to or have contraindications for treatment with other pharmacologic agents. Treatment with non-pharmacologic modalities should be continued in these patients, and appropriate surgical options should be considered.
18. Osteotomy can be applied in middle-aged, active, unicompartmental knee OA patients with malalignment for the aim of biomechanical correction.
19. Total knee replacement should be considered for patients with advanced knee OA who have resistant pain to pharmacologic and non-pharmacologic treatments and impaired quality of life. Not only the radiologic images but also the degree of pain and functional limitation of patients should be taken into consideration during the course of decision for surgery.

Table 4. TLAR recommendations with level of evidence, consensus rate and strength of recommendations

Recommendations	LOE	Consensus (%)	SOR % (95% CI)
1. The main goal in the treatment of knee OA should be directed toward controlling pain, preserving and improving the function of joints, providing functional independency, and increasing the quality of life. In order to reach these goals, management of knee OA should contain non-pharmacologic, pharmacologic, and, when necessary, surgical approaches. Treatment should be tailored for each patient individually.	IV	77.3	96.8 (93-100)
2. Educational programs about the symptoms of the disease, composition, and treatment objectives, designed for individuals and patient groups, may increase the adherence of patients to the therapy. These educational programs should contain lifestyle alterations, joint protection techniques, and diet and exercise programs which would provide weight control.	Ib, III	77.3	95.7 (94-98)
3. Patients with knee OA should be informed and encouraged to use their joints in a manner that allows the least amount of loading on their joints during their occupational, sports, and daily living activities. They should be educated to make this a principle part of their daily lives. The conditions at their home and office should be designed according to their disease. Patients should be advised to avoid climbing stairs, sitting cross-legged, squatting, kneeling during "namaz (an Islamic prayer)" or doing any other activity which would cause loading and enforcement of knee flexion. Using elevators, sitting without knee flexion during "namaz", and using a Western-style toilet should be advised instead.	III, IV	63.6	94.0 (91-97)
4. Age, comorbid diseases, and degree of OA should be taken into consideration when choosing an appropriate exercise program for each individual patient. Patients should be encouraged to do range-of-motion, stretching, isometric, isotonic, balance, proprioception, and aerobic exercises. Aquatic exercises can be planned in concert with the preferences of the patient and physician. The exercise programs should be taught to patients in a manner that they can clearly understand and be able to do on their own. Initially, they should be under supervision, but when the patients are able to do them by themselves, home programs should be started.	Ia, Ib	77.3	96.6 (95-98)
5. Physical medicine and rehabilitation specialists may advise the use of an appropriate walking stick, walker, or similar walking aid after the evaluation of the patients. These devices may decrease the patients' pain levels; therefore, they should be educated regarding the correct use of these devices.	Ib	90.9	96.5 (95-98)
6. In knee OA patients with mild to moderate joint instability, the use of appropriate ortheses may decrease the risk of falling and may help to restore the stability. Each patient should be advised to choose convenient, comfortable, soft-soled shoes. The use of sole plates may help ambulation by decreasing pain in patients with knee OA. The application of a laterally-wedged insole in the shoes may have a symptomatic benefit in patients with medial tibiofemoral OA.	Ia, III, IV, Ib	90.9	86.4 (80-93)
7. Electrotherapeutic agents such as TENS, interferential currents, and diadynamic currents may have beneficial effects on pain, joint function, and quality of life. Superficial and deep heat (ultrasound, short wave diathermy) applications may provide benefits for patients with knee OA who have no active synovitis. Cold application should be advised in the case of synovitis.	Ib, Ia, III	72.7	96.6 (94-99)
8. Neuromuscular electrical stimulation is one of the physical treatment modalities- considered not only for muscle strengthening but also as an alternative modality for alleviating the pain and functions of patients who are not able to take part in exercise programs.	III, Ia	72.7	88.1 (82-94)
9. If there is no contraindication, balneotherapy may be recommended for at least two weeks of treatment because of its thermal and non-thermal effects. Patients who are advised to have balneotherapy should be informed about the thermal and mineral aspects of the water of the center that they plan to attend. In addition to this treatment, peloidotherapy may be advised. Balneotherapy may be combined with other physical treatment modalities and exercises by a PM&R specialist.	Ia, Ib, III	86.4	91.2 (87-95)
10. Complementary treatment options should not be used instead of standard pharmacologic and non-pharmacologic treatments. But if it would be, it should only be used as an additional treatment. Both the beneficial and adverse effects of complementary treatments should be followed carefully.	Ia	77.3	93.6 (89-98)
11. Acetaminophen (maximum 3 g/day) as an initial treatment may have a mild analgesic effect in patients with knee OA who have a mild/moderate degree of pain. Alternative treatment options should be considered in case of inadequate response or the presence of severe pain and/or inflammation.	Ia, III	77.3	90.6 (83-98)
12. Nonselective and selective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors should be used at their lowest efficacious doses for conditions in which there is moderate to severe pain or synovitis and for situations in which paracetamol is insufficient. Concomitant use of two NSAIDs should be avoided. Gastroprotective agents should be combined with NSAIDs in patients with gastrointestinal complaints. Precaution should be taken with the use of NSAIDs if hypertension exists or renal or hepatic dysfunction are present.	Ia, Ib, IIb	77.3	95.9 (94-98)
13. Topical NSAIDs or capsaicin can be used in combination with other analgesic and/or anti-inflammatory drugs, or they can be used on their own if patients are unable to take other drugs.	Ia	81.8	95.5 (92-99)
14. Intraarticular glucocorticoid injection, not more than three times a year, can be applied in cases of symptomatic knee OA with signs of inflammation which are unresponsive to other treatment options.	Ia	72.7	97.0 (95-99)
15. Hyaluronic acid injections may be beneficial for patients with mild and moderate OA who are not overweight, have no instability, and are unresponsive to non-pharmacologic and pharmacologic treatment modalities.	Ia, Ib, III	90.9	88.8 (83-95)
16. Glucosamines and/or chondroitin sulfate may provide symptomatic benefits for patients with knee OA.	Ia, IIb, Ib	72.7	87.3 (80-95)
17. Administration of weak opioids or narcotic analgesics can be considered for patients with knee OA who are resistant to or have contraindications for treatment with other pharmacologic agents. Treatment with non-pharmacologic modalities should be continued in these patients, and appropriate surgical options should be considered.	Ia	63.6	86.8 (80-93)
18. Osteotomy can be applied in middle-aged, active, unicompartmental knee OA patients with malalignment for the aim of biomechanical correction.	IIa	90.9	86.9 (80-94)
19. Total knee replacement should be considered for patients with advanced knee OA who have resistant pain to pharmacologic and non-pharmacologic treatments and impaired quality of life. Not only the radiologic images but also the degree of pain and functional limitation of patients should be taken into consideration during the course of decision for surgery.	III	90.9	89.2 (84-95)

LOE: Level of evidence; SOR: Strength of recommendation.

General Principles

1. The main goal in the treatment of knee OA should be directed toward controlling pain, preserving and improving the function of joints, providing functional independency, and increasing the quality of life. In order to reach these goals, management of knee OA should contain non-pharmacologic, pharmacologic, and, when necessary, surgical approaches. Treatment should be tailored for each patient individually.

The daily clinical practice for the management of knee OA is a combination of pharmacologic and non-pharmacologic treatment options. The main goal of all these approaches is to decrease pain and ameliorate the functional capacity of the patients. This is a generally accepted proposition although there is no clinical trial evidence to support it. It was included in all previously published guidelines even though the LOE is IV.^[2-5] Similarly, the majority of the experts voted in favor of accepting this recommendation during the Delphi tours of our study, and the SOR was 96.8% (95% CI 93-100).

Non-Pharmacologic Treatment

2. Educational programs about the symptoms of the disease, composition, and treatment objectives, designed for individuals and patient groups, may increase the adherence of patients to the therapy. These educational programs should contain lifestyle alterations, joint protection techniques, and diet and exercise programs which would provide weight control.

The instructional programs, which include lifestyle alteration, joint protection principles, and suggestions for weight reduction, are contained in the main guidelines for patients with knee OA. These programs can be given individually or as group education, the latter being less expensive. Group education followed up by home exercise programs has been shown to restore functional capacity and improve pain levels (LOE Ib).^[12] Obesity is considered to be a risk factor for symptomatic knee OA. Each 3 or 4 kg/m² increase in body mass index (BMI) doubles the risk of OA.^[13] Weight reduction was strongly recommended in previous guidelines, even though controversy existed about the relationship between weight reduction and clinical symptoms.^[2-5] In a recently published report, a 10% reduction of weight in obese individuals showed significant improvement in the symptoms of knee OA (LOE III).^[14] Bliddal et al.^[15] reported that an 11% weight reduction in overweight patients provided a

small but significant degree of reduction in pain associated with symptomatic knee OA (LOE Ib). Thus, an education program that includes weight control for the patients has great importance. The experts strongly recommended this proposition (SOR 95.7%, 95% CI 94-98).

3. Patients with knee OA should be informed and encouraged to use their joints in a manner that allows the least amount of loading on their joints during their occupational, sports, and daily living activities. They should be educated to make this a principle part of their daily lives. The conditions at their home and office should be designed according to their disease. Patients should be advised to avoid climbing stairs, sitting cross-legged, squatting, kneeling during "namaz (an Islamic prayer)" or doing any other activity which would cause loading and enforcement of knee flexion. Using elevators, sitting without knee flexion during "namaz", and using a Western-style toilet should be advised instead.

Modification of daily living activities is an important component of non-pharmacologic treatment options for management of knee OA. Additionally, patients should learn joint protection principles for when they do occupational activities or participate in sports. Activities which put pressure on the knee might aggravate symptoms in a dose/response manner.^[16] Squatting or bending of the knee and similar activities were reported to possibly contribute to the development of symptomatic knee OA in both genders (OR was 2.5%, 95% CI 1.4-4.7; and 2.2 % 95% CI 1.2-3.8 for females and males, respectively). Particularly with obesity and load lifting activities, the risk was even higher.^[13,16] In an epidemiological survey, no association was found between "namaz" and symptomatic knee OA (LOE III).^[1] More comprehensive investigations concerning these issues are needed. In light of present scientific data, to avoid knee flexion, using alternative positions during "namaz" might be more beneficial (LOE IV). Patients should also be instructed to modify their sitting positions along with their use of stairs and the toilet, although there is no adequate evidence to support this approach.^[16] This proposition was strongly recommended (SOR 94%, 95% CI 91-97).

4. Age, comorbid diseases, and degree of OA should be taken into consideration when choosing an appropriate exercise program for each individual patient. Patients should be encouraged to do range-of-motion, stretching, isometric, isotonic, balance, proprioception, and aerobic exercises. Aquatic

exercises can be planned in concert with the preferences of the patient and physician. The exercise programs should be taught to patients in a manner that they can clearly understand and be able to do on their own. Initially, they should be under supervision, but when the patients are able to do them by themselves, home programs should be started.

Exercise protocols should be tailored according to the clinical aspects and individual needs of each patient. The importance of exercise treatments has been emphasized in previous recommendations and guidelines.^[2-6] In an RCT, no difference between behavioral activity and normal exercise therapy was found in the long-term primary outcome measures of OA.^[17] It was reported that progressive resistive exercises improved physical activity and reduced pain in patients with knee OA (LOE Ib).^[18] Tai Chi exercises might be considered as an optional treatment choice since they are safe and effective on pain and function, although there is no significant scientific evidence to prove its benefits.^[19] Aquatic exercises were not deemed to be superior when compared with other types of exercises, but they might be preferred due to less pain occurring after exercise.^[20] According to the results of an RCT which compared the effects of loading and non-loading exercises, simple flexion-extension exercises for an eight-week period provided significant functional improvement for patients using either type of exercises; however, the beneficial effect in position sensation was shown only in the group doing the loading exercises (LOE Ib).^[21] In another RCT, simple strengthening exercises designed as a home program provided significant pain relief and functional improvement in long-term follow-up. As a result of this study, weight reduction was found to have no benefit on pain, but it improved depression (LOE Ib).^[22] A pilot study was performed in our country concerning the results of Pilates exercises which were designed as group and home exercise programs. This study showed that these exercises led to improvement in many clinical parameters, especially when performed as group therapy.^[23] Lin et al.^[24] reported significant improvement in pain and functional Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in an RCT in which strengthening and proprioceptive exercises without loading were compared (LOE Ib). Progressive resistive training programs were found to have beneficial effects on physical activities, especially in those patients with early OA.^[18] Significant improvement in pain and functional capacity was shown when performing concentric-

eccentric isokinetic training for the quadriceps muscle (LOE Ib).^[25,26] There are many kinds of exercises for the treatment of knee OA. A detailed evaluation of the patient along with an appropriate choice of exercise with respect to the patient's needs are crucial. The LOE was good, and the SOR was high for this proposition (SOR 97%; CI 95-98).

5. Physical medicine and rehabilitation specialists may advise the use of an appropriate walking stick, walker, or similar walking aid after the evaluation of the patients. These devices may decrease the patients' pain levels; therefore, they should be educated regarding the correct use of these devices.

Patients with knee OA may have difficulty in walking due to a variety of factors. Patients generally transmit almost all body weight to the medial compartment of the knee joint. Reduction of the loading over this site may be an important treatment goal. Use of walking sticks may be recommended for this purpose. A study which evaluated the effect of using walking sticks revealed that for patients who used them for two months, a small but significant amount of improvement occurred in their pain and function (effect sizes 0.18, 95% CI -0.42-0.87 and 0.13, 95% CI -0.11-0.42, respectively) (LOE Ib).^[27] If involvement is unilateral, sticks or crutches should be used contralaterally. In case of bilateral involvement, simple walkers or walkers with rollers should be the preference. This proposition has no supportive evidence at the RCT level, but our experts strongly recommended it, and the SOR was high (96.4%, 95% CI 95-98).

6. In knee OA patients with mild to moderate joint instability, the use of appropriate orthoses may decrease the risk of falling and may help to restore the stability. Each patient should be advised to choose convenient, comfortable, soft-soled shoes. The use of sole plates may help ambulation by decreasing pain in patients with knee OA. The application of a laterally-wedged insole in the shoes may have a symptomatic benefit in patients with medial tibiofemoral OA.

This proposition is also present in the 2008 OARSI recommendations. Based on a brace study, the authors concluded that if a brace or sleeve application was compared with medical therapy alone, there was limited evidence of additional beneficial effects on pain and function, with the brace being more effective than sleeve (LOE Ia).^[2] In an SR which was published after this report, non-randomized trials were also analyzed.^[28] It was concluded that compressive

loading over the medial tibial compartment might be decreased, proprioception might be improved, and the isokinetic power of the quadriceps muscle might be increased by using a valgus brace (LOE III). A short-to-medium period of using the valgus brace might provide pain relief and improve quality of life, but the effect range of this device is variable, and it is difficult and uncomfortable to use.

In a study performed in our country, the authors reported that medial taping of the patella was superior to other medical therapies in patellofemoral OA (LOE III).^[29]

Recommending the use of appropriate shoes is not supported by evidence in controlled trials. Instead, it was recommended based on expert opinions (LOE IV).

Laterally-wedged insole application for medial tibiofemoral OA was recommended by many guidelines, and there are many trials concerning this issue. Two RCTs were published after the 2010 update of the OARSI recommendations. In the first trial performed in our country, the effects of laterally-wedged insole application on pain and function was evaluated in patients with knee OA. As a result, it was found that it was superior to medical therapy consisting of analgesics and exercise (LOE Ib).^[30] In the other RCT, the effects of laterally-wedged insole application was compared with the use of the valgus brace. Both treatment modalities led to a significant reduction in pain, but neither was superior to the other (LOE Ib).^[31] The strength of recommendation was moderate for this proposition (SOR 86.4%, 95% CI 80-93).

7. Electrotherapeutic agents such as TENS, interferential currents, and diadynamic currents may have beneficial effects on pain, joint function, and quality of life. Superficial and deep heat (ultrasound, short wave diathermy) applications may provide benefits for patients with knee OA who have no active synovitis. Cold application should be advised in the case of synovitis.

Physical treatment modalities are widely used and preferred by patients with knee OA. Superficial and deep heaters along with analgesic currents may be the only treatment options, especially for elderly patients who are potentially intolerant to drugs. Physical modalities are recommended by all guidelines for the management of knee OA.^[2-5] The number of RCTs regarding the effects of these agents is not sufficient. In a study performed in our country, a combination of hot pack, transcutaneous electrical nerve stimulation (TENS),

therapeutic ultrasound, quadriceps strengthening exercises, and diclofenac was compared with the use of diclofenac alone. After completion of a 10-day session, painless walking distance and daily living activities showed greater improvement in the group having a combination of physical agents (LOE Ib).^[32] In another study, the effects of a combination of ultrasound and TENS combined with exercises was found to be superior to exercise therapy alone on the restoration of balance (LOE Ib).^[33] The 2008 OARSI recommendations and many other guidelines have recommended the use of TENS for knee OA. The efficiency of TENS by itself on pain and joint function in knee OA was evaluated in an SR and was found to be insignificant.^[34] The heterogeneity and inadequate number of patients within the evaluated trials were the weaknesses of this SR, and the necessity for well-designed trials was emphasized. According to a recent study, an RCT with a combination of exercises, hot compresses, and TENS created better results on pain and quality of life scores than the same combination with sham TENS application (LOE Ib).^[35] Transcutaneous electrical nerve stimulation, diadynamic currents or interferential currents are thought to produce analgesia. These modalities were investigated in combination with exercise and/or heat applications in general. Therefore, the pure efficiency of these currents could not be estimated individually. However, combination therapy is used in daily practice.

Superficial and deep heating modalities are widely used in the management of knee OA. According to the 2010 OARSI update, application of any thermal modality in patients with knee OA is also recommended in the majority of guidelines.^[6] Mechanical vibrations, continuous passive motion, and thermal applications in combination with other treatments were reported to provide significant improvement in pain and functions (LOE Ib).^[36]

The application of therapeutic ultrasound was found to be effective for providing symptomatic and functional improvements in knee OA in two MA, but the heterogeneity of the methods and weaknesses in the level of evidence of evaluated trials created difficulty in predicting the effect size of this modality (LOE Ia).^[37,38] In a study performed in our country, the authors showed that an exercise program combined either with ultrasound or short-wave diathermy had significant beneficial effects on pain and function. However, the low number of subjects and lack of a control group were limitations of this study (LOE III).^[39] The application of a 10-session

therapeutic ultrasound was compared with sham in another RCT, and a significant reduction in pain scores (48%) together with significant improvements in the total WOMAC score and 50-meter walking time were found (LOE Ib).^[40]

Pulsed electromagnetic field treatment for knee OA was evaluated in a small trial, and a significant improvement in WOMAC scores was reported (LOE Ib).^[41] Based on nine trials with 483 patients, the authors concluded that pulsed electromagnetic field therapy improved pain and stiffness scores in patients with knee OA, but not significantly. In contrast, the daily living activities and functional scores improved significantly (LOE Ia).^[42] It was shown that pulsed electromagnetic field therapy was not superior to conventional physical therapy (LOE Ib).^[43] Pulsed electromagnetic field treatment did not exist in guidelines published before the 2010 update of the OARSI recommendations.^[6] In summary, the beneficial effect of pulsed electromagnetic field therapy is evident with respect to function functions, but it is not as clear considering on pain.

Iontophoresis and phonophoresis may improve pain and functional activities. Applications of ibuprofen iontophoresis and phonophoresis were found to significantly improve pain and functional levels when compared with the initial findings, but no difference was evident between the two modalities.^[44,45] This proposition consisted of a variety of physical agents with different levels of evidence, and our experts recommended it strongly (SOR 96.5%, 95% CI 94-99).

8. Neuromuscular electrical stimulation is one of the physical treatment modalities- considered not only for muscle strenghtening but also as an alternative modality for alleviating the pain and functions of patients who are not able to take part in exercise programs.

In studies in which the effects of neuromuscular electrical stimulation and isometric exercise of the quadriceps muscle were compared, it was shown that both modalities provide improvement in pain and function related to the initial level. However, the patients who received electrical stimulation had greater improvement, especially in walking capacity.^[46-48] In these studies, other treatment modalities, such as superficial heating and TENS, were also used. An enlargement in the mass and an increase in the perfusion of the quadriceps muscle were demonstrated by computed tomography (CT) and scintigraphy (LOE III). Neuromuscular electrical stimulation is

widely used in the early period after an arthroplasty operation. In an MA, it was mentioned that the evidence level of studies related to electrical stimulation was low, so the effect should be accepted with caution (LOE Ia).^[49] The SOR of this proposition was 88,1% (95% CI 82-94).

9. If there is no contraindication, balneotherapy may be recommended for at least two weeks of treatment because of its thermal and non-thermal effects. Patients who are advised to have balneotherapy should be informed about the thermal and mineral aspects of the water of the center that they plan to attend. In addition to this treatment, peloidotherapy may be advised. Balneotherapy may be combined with other physical treatment modalities and exercises by a PM&R specialist.

Balneotherapy and mineral water baths are non-pharmacologic options that have been used for the treatment of knee OA for a long time. In an SR (LOE Ia), the results of nine RCTs with a total of 493 patients who completed 10-24 weeks of treatment duration were evaluated. It was concluded that the scores of pain and functional capacity were improved, and this improvement lasted for 24 weeks. It was also decided that balneotherapy can be considered as a safe and effective option when used as part of a multidisciplinary approach for the management of knee OA.^[50] Forestier et al.^[51] reported that a three-week period of spa treatment combined with a pharmacologic and home exercise program was superior to conventional treatments and exercise alone at the end of sixth month, and it was better tolerated (LOE Ib). A trial performed in Gönen/Balıkesir demonstrated that 20 minutes of treatment duration applied twice daily for two weeks improved walking time as well as the general health quality in patients with knee OA (LOE III).^[52] Any patient directed to balneotherapy should be informed concerning its potential effects, especially the “thermal crisis”, of this treatment option. The presence of a PM&R specialist in balneotherapy centers may decrease such potential adverse events. Additionally, a combination of balneotherapy with physical agents and exercises can also be performed (SOR was 91.2, 95% CI 87-95).

10. Complementary treatment options should not be used instead of standard pharmacologic and non-pharmacologic treatments. But if it would be, it should only be used as an additional treatment. Both the beneficial and adverse effects of complementary treatments should be followed carefully.

Acupuncture, which has been accepted as an alternative or complementary treatment option, was considered as a separate proposition in the 2008 OARSI recommendations, but the SOR was low (59%; 95% CI 47-71).^[2] Acupuncture was not mentioned in the NICE and AAOS guidelines.^[4,5] The beneficial effects of acupuncture were shown in sham-controlled studies, but the level of evidence and the quality of evaluated trials were not sufficient (LOE Ia).^[53] The clinical effectiveness of acupuncture application might vary depending on the technique used by the person performing, and some of the neurophysiologic alterations attributed to acupuncture might be considered to be a placebo effect.^[54] The SOR of this proposition was 93.6%, (95% CI 89-91).

Pharmacologic Treatment

11. Acetaminophen (maximum 3 g/day) as an initial treatment may have a mild analgesic effect in patients with knee OA who have a mild/moderate degree of pain. Alternative treatment options should be considered in case of inadequate response or the presence of severe pain and/or inflammation.

Acetaminophen was accepted as the first drug of choice in the treatment of knee OA by many of the guidelines.^[2-5] In the updated 2010 OARSI recommendations, as a result of a cumulative meta-analytic evaluation, the effect size of analgesia provided by acetaminophen was found to be low but significant. In addition, it was concluded that acetaminophen had no effect on stiffness and function of the joint (LOE Ia).^[6] There is controversy concerning the recommended acetaminophen dose. Four grams per day was suggested by the 2008 OARSI recommendations.^[2] According to more recent trials, consumption of acetaminophen at a dose higher than 3 g/day might be associated with a high risk of gastrointestinal complications, and long-term consumption could cause hypertension and impairment in renal functions.^[55,56] In our recommendations, the suggested maximum dose for acetaminophen is 3 g/day. Using slow-release acetaminophen might increase the compliance (LOE III).^[57] The SOR was 90.6% (95% CI 83-98).

12. Nonselective and selective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX-2) inhibitors should be used at their lowest efficacious doses for conditions in which there is moderate to severe pain or synovitis and for situations in which paracetamol is insufficient. Concomitant use of two NSAIDs should be avoided. Gastroprotective

agents should be combined with NSAIDs in patients with gastrointestinal complaints. Precaution should be taken with the use of NSAIDs if hypertension exists or renal or hepatic dysfunction are present.

When symptomatic knee OA has been unresponsive to paracetamol, NSAIDs have been recommended by almost all of the guidelines or recommendations. According to previous investigations, the effect size for the analgesia provided by NSAIDs was reported to be between 0.20-0.29 (LOE Ia).^[6] In an RCT (LOE Ib), the analgesic effect of diflunisal was evaluated and was reported to be superior to a placebo.^[58] After the 2010 update, three RCTs concerning new NSAIDs were published (LOE Ib). In the first RCT, S-adenosylmethionine and nabumetone were compared in an eight-week study. With both drugs, a significant reduction in pain scores was found when compared with the initial findings, with no difference between the two drugs.^[59] In the second trial, the effects of naproxinod were compared with naproxen and placebo.^[60] Naproxinod and naproxen provided significant improvement in pain and function over the placebo. The systemic blood pressure was found to be higher among patients using naproxen while there was not any difference between the placebo and naproxinod. In a trial (LOE IIb), patients who were candidates for total knee replacement (TKR) surgery were treated either with celecoxib or indomethacin for a four-week period prior to the procedure, and cartilage and synovial samples were evaluated after the surgery.^[61] Proteoglycan synthesis was found to be significantly increased among celecoxib users but not in the indomethacin and control groups. Prostaglandin E 2 (PGE 2) levels were found to be lower in the patients who used either of the drugs when compared with the controls. The indomethacin and celecoxib groups had lower levels of interleukin-1beta (IL-1 β) while the latter group also had lower levels of tumor necrosis factor-alpha (TNF- α). In order to prevent the potential adverse effects of NSAIDs on the gastrointestinal system, concomitant use of misoprostol or proton pump inhibitors were included in almost all of the guidelines. The use of COX-2 specific inhibitors was also recommended for patients with a gastrointestinal risk (LOE Ib).^[2-5] In our country, however, COX-2 inhibitors are not officially permitted. On the other hand, potential adverse cardiovascular events related to COX-2 inhibitors have been demonstrated by several reports, with the presence of ischemic heart disease or history of stroke being defined as contraindications for COX-2 inhibitors.^[6] These drugs should be used

with caution in patients with hypertension, diabetes mellitus, hyperlipidemia, peripheral arterial disease, or in those who smoke or have other similar risk factors. This proposition was strongly recommended (SOR 95.8%, 95% CI 94-98).

13. Topical NSAIDs or capsaicin can be used in combination with other analgesic and/or anti-inflammatory drugs, or they can be used on their own if patients are unable to take other drugs.

Topical NSAIDs are widely used by patients with knee OA, and their use is recommended by many guidelines, including the 2008 OARSI recommendations.^[2-5] The effects of these drugs on pain and stiffness were found to be moderate and superior to placebo, but analyzed trials were highly heterogeneous (LOE Ia).^[2] The adverse event occurrence was not different than for the placebo. Capsaicin is a lipophilic alkaloid extracted from chili peppers. It is considered to be effective over nociceptive receptors. It is recommended to be applied topically four times per day over the painful joint. No significant side effects, other than itching or a burning sensation on the site of application, have been reported. The SOR was 95.5% (95% CI 92-99) for this proposition.

14. Intraarticular glucocorticoid injection, not more than three times a year, can be applied in cases of symptomatic knee OA with signs of inflammation which are unresponsive to other treatment options.

Intraarticular glucocorticoid administration has been widely used for a long period of time for the management of knee OA. It has been recommended by a variety of guidelines, including the 2008 OARSI recommendations.^[2-5] The effect size was reported as 0.58 (95% CI 0.34-0.82) with intraarticular administrations from the first to the third weeks. The NNT was 5 (95% CI 3-38) (LOE Ia).^[62] The beneficial effects of intraarticular glucocorticoids seem to disappear by the end of the fourth week. No significant adverse effects have been reported. Their use has been recommended especially for patients with inflammatory findings. Patients should be instructed not to overuse their joints after the injection in order to prevent accelerated progression of the disease. The evidence level was high, and our experts supported this proposition strongly (SOR 97%, 95% CI 95-99).

15. Hyaluronic acid injections may be beneficial for patients with mild and moderate OA who are not overweight, have no instability, and are unresponsive to non-pharmacologic and pharmacologic treatment modalities.

Intraarticular administration of hyaluronic acid (IHA) is used extensively for treatment of knee OA, despite controversies regarding its efficiency. This proposition did not exist in the NICE guideline, and the controversies were emphasized in the AAOS.^[4,5] Zhang et al.^[6] evaluated the trials related to IHA until 2009, and they mentioned that the studies were done with different formulations, performed weekly for three to five times weekly, and compared either with placebo or glucocorticoids. The efficiency was prompted at the first through the fourth weeks of treatment (LOE Ia). The effect sizes for pain relief along with improvement in function and stiffness were found to be moderate when compared with the placebo (0.60, 95% CI 0.35-0.87, 0.61, 95% CI 0.37-0.83 and 0.54, 95% CI 0.17-1.26, respectively). The NNT was 7 (95% CI 3-119). They also emphasized that the trials were heterogeneous. When an elimination was carried out according to the Jadad quality score, no significant difference was found in the pain scores. Pain relief occurred earlier in the glucocorticoid group (2-4 weeks) while requiring much more time in the IHA group (5-13 weeks). There is no MA concerning the effects of IHA published after 2009. According to an RCT, an application of 6 ml of hylan GF (instead of weekly injections) provided pain relief at the 26th week of administration (LOE Ib). No difference was reported between these two applications with respect to adverse events.^[63] In another study, the effects of intraarticular administrations of glucocorticoids and IHA were compared, and no significant clinical differences were found.^[64] The synovial fluid examination revealed a significant increase in the levels of sodium hyaluronate (Na-HA) and a significant decrease in the levels of matrix metalloproteinase-9 in the patients treated with IHA. It was suggested that IHA not only had a protective effect on articular cartilage but also an inhibitor effect on catabolism (LOE III). In a one-year follow-up study, after five consecutive weeks of IHA administration in 337 subjects, pain, function, and the need for paracetamol consumption were evaluated at three, six, nine and 12 months. The results were found to be no better than placebo (LOE Ib).^[65] There have been a number of trials performed in our country on this subject. In one of these, five consecutive weeks of IHA administration in patients with knee OA was evaluated, and the results were also found to be no better than placebo (LOE Ib).^[66] In the second trial, IHA administration was performed for patients with synovitis, and the results at the end of first year were found to be better than placebo.^[67] In the patients who had been treated with IHA, short-term improvement

in proprioception and isokinetic muscle strength along with significant improvement in function were also reported (LOE Ib).^[68] In brief, the trials concerning the effects of IHA are heterogenous. Their application may provide a beneficial effect by selecting appropriate patients. The SOR was 88.8%, (95% CI 83-95).

16. Glucosamines and/or chondroitin sulfate may provide symptomatic benefits for patients with knee OA.

Glucosamine sulphate (GS) and chondroitin sulphate (CS) are complex sugars within the natural structure of articular cartilage. Both molecules are prepared for oral consumption and partially absorbed in the small intestine. It was reported that they could be detected in synovial fluid as well as serum after administration.^[69] They have been used by patients with knee OA extensively and have been preferred by many physicians interested in OA, particularly in the last 10 years. The recommended dose for GS is 1500 mg/day for six weeks with a one-week break, and it should be stopped if there is no response at the end of six months. There are a number of studies concerning the use of GS and CS, but their efficacy is still controversial. It is also not clear whether these agents modify the structure of articular cartilage or not. While administration of GS was recommended in several guidelines concerning the management of knee OA, CS existed only in a few of them. Neither of the molecules was recommended in the NICE and AAOS guidelines.^[3,4] The use of GS and CS in knee OA, which was in the 2008 OARSI recommendations, was dependent on a Cochrane review published in 2005, but variability in the formulations were not taken into account.^[70] In the 2010 update of the OARSI recommendations, the therapeutic effects of GS and glucosamine hydrochloride (GH) were analyzed separately.^[6] The authors suggested that the efficiency of GH on pain was small and statistically insignificant. The studies related to GS were heterogenous, and when they were evaluated according to quality, the effect size for pain was found to also be small but significant (0.29, 95% CI 0.0003-0.57) (LOE Ia). The heterogeneity of the studies was a major problem. The studies concerning the effects of CS were also heterogenous. The results of these studies, if analyzed in accordance with quality assessment, indicated that the effect on pain was small and insignificant. No significant adverse event was reported (RR/OR= 0.97 and 0.99) (LOE Ia).^[6] In two MAs, the long-term effects of GS and CS were evaluated based on the modification of the structure and progression of the joints.^[71,72] In

one MA based on six RCTs, Lee et al.^[71] analyzed a total of 1502 patients and concluded that no significant differences were found in joint space narrowing by the end of the first year in patients who used GS, and a small to moderate difference was observed in the third year of treatment (effect size 0.43, 95% CI 0.24-0.63) (LOE Ia). Similarly, patients who used CS had a small but significant difference in joint space by the end of the second year (effect size 0.26, 95% CI 0.13-0.39). As a result of this MA, the authors suggested that administration of GS for three years and CS for two years might delay the radiologic progression of the disease.^[71] In the other MA, the results of two RCTs were analyzed, and the authors concluded that a small but significant difference in joint space narrowing was found in the patients taking CS 800 mg/day for two years when compared with placebo (effect size 0.23, 95% CI 0.11-0.35).^[72] In one of the studies from this MA, Kahan et al.^[73] suggested that pain relief was significant and occurred faster in patients using CS compared with the placebo, and this was observed as early as the sixth month of therapy. The NNT was found to be 8 (95% CI 5-17), and no adverse event was reported. No significant effect on joint space narrowing was shown in a small sample-sized study with the use of GH.^[74] In another trial with LOE IIb, GS administration delayed the development of OA when compared with placebo in rats and decreased nociception. The authors reported that modification of chondrocyte metabolism might possibly have occurred by increasing the inhibition of the p38 kinase and the c-Jun N terminal kinase (JNK) or by increasing the release of an extracellular signal-related kinase (ERK).^[75] In another RCT (LOE Ib), cartilage turnover was evaluated, and patients on a quadriceps strengthening exercise program for 12 weeks were given either GS 1500 mg/ day, ibuprofen 1200 mg/day, or placebo. A significant decrease in the serum level of cartilage oligometric protein (COMP) was determined in the patients taking GS.^[76] According to the results of a two-year follow-up study in which the effects of GH at a dose of 1500 mg/day, CS 1200 mg/day, celecoxib 200 mg/day and placebo were compared, no superiority on the WOMAC pain scores was found in GS and CS users compared with celecoxib and the placebo (LOE Ib).^[77] In a five-year observational study, total knee replacement (TKR) was found to be less frequent among patients who had taken GS for at least 12 months compared with placebo.^[78] It should be kept in mind, however, that there are various factors which would affect the indication for TKR. As one can see, there is still much controversy regarding the efficacy of these molecules.

Although there is no evidence concerning the provocation of diabetes mellitus or asthma with the consumption of glucosamines, precaution should be taken if the drug is used in high risk patients. An MA evaluating this issue was published in 2011 based on 11 trials (six RCTs and five prospective trials).^[79] A significant affect of glucosamines on glucose metabolism was shown in two RCTs. In several trials performed in obese patients, an affect was found on glucose metabolism while no affect was found in patients with diabetes mellitus. However, the formulations of the glucosamines were not mentioned, and administration was heterogenous (single or divided daily doses). The types of laboratory tests used for glucose metabolism were also not identical. Thus, further investigation is required. It should not be ignored that these molecules might provoke latent diabetes.

Glucosamines are also present in combinations that include other nutraceuticals in the market. According to a study performed in Italy, the amount and quality of the CS in these nutraceuticals varied. The authors emphasized that the health authority did not have strict regulations regarding manufacturers and controllers.^[80] This is, of course, not only a problem of Italy, but also of our country beside many others. This controversial proposition consisting of heterogenous trials was moderately supported by our experts (SOR 87.3%; 95% CI 80-95).

17. Administration of weak opioids or narcotic analgesics can be considered for patients with knee OA who are resistant to or have contraindications for treatment with other pharmacologic agents. Treatment with non-pharmacologic modalities should be continued in these patients, and appropriate surgical options should be considered.

Treatment with opioids was recommended in almost all guidelines, including the 2008 OARSI recommendations.^[2-5] In an MA, the effect size of opioid treatment on pain and functional scores were reported as 0.78 (95% CI 0.59-0.98) and 0.31 (95% CI 0.24-0.39), respectively (LOE Ia).^[81] However, the trials were heterogenous with respect to methods and formulations in general. Nausea, constipation, sleep disturbance, dizziness, and vomiting are widely encountered adverse effects associated with opioid therapy, and these are the major causes for the discontinuation of the drug. There is no data concerning the long-term use of these drugs, especially related to dependence. For patients with moderate to severe pain, a significant

reduction in pain and improvement in function might be achieved by the administration of tramadol once a day (LOE Ia).^[82] In a Cochrane review published in 2009, the advantages and disadvantages of opioid therapy (oral or transdermal) were compared versus placebo in patients with knee or hip OA (LOE Ia). Various kinds of opioid formulations were superior when compared with the placebo, but there were no differences between the two types of opioid therapy.^[83] The authors concluded that non-tramadol opioids had significant low to moderate benefits but that significant adverse effects also existed. They suggested that these formulations should not be used, even in cases suffering from severe pain. Weak opioids, such as tramadol, tramadol/paracetamol, codeine, and propoxyphen, should be preferred initially in resistant cases in which other types of treatments could not be applied. The stronger opioids, such as oxymorphone, oxycodone, phentanyl, and morphine sulphate, should be reserved for extraordinary conditions. The SOR was moderate (86.8%, 95% CI 80-93).

Surgical Treatment

18. Osteotomy can be applied in middle-aged, active, unicompartamental knee OA patients with malalignment for the aim of biomechanical correction.

Based on a Cochrane SR, the authors mentioned some beneficial effects of high tibial osteotomy (HTO) on pain and function, despite there being no study which has compared the efficacy and safety of an osteotomy with a placebo or conservative treatment in unicompartamental knee OA (LOE IIa).^[84] It is difficult to compare and evaluate the results of studies concerning this procedure since there are various techniques used for a high tibial osteotomy. In another SR, unicompartamental knee arthroplasty (UKA) was compared with HTO and TKR.^[85] The results were found to be similar with respect to function, but complications, such as deep venous thrombosis, were reported less frequently after UKA (not statistically significant), and revision rates were lower when compared with HTO. In brief, HTO and UKA can be accepted as surgical options for relatively young patients with involvement of the medial compartment, but the results are still controversial. There were no comparative trials with conservative treatments. The different surgical techniques used in the trials made a comparison difficult. Selecting the right patient and taking him/her expectations into account are thought to be important for positive outcome. It was reported that only a small number of patients with knee OA could be

described as right candidates for this type of surgical approach (being 60-65 years old, moderately active, non-obese, having 5-10 degrees of varus malalignment, with no instability and no limitation in range of motion and with moderate unicompartamental involvement).^[86] The subject is still a matter of discussion, and more comprehensive studies are required. This proposition was supported moderately by the committee (SOR 86.9%, 95% CI 80-94).

19. Total knee replacement should be considered for patients with advanced knee OA who have resistant pain to pharmacologic and non-pharmacologic treatments and impaired quality of life. Not only the radiologic images but also the degree of pain and functional limitation of patients should be taken into consideration during the course of decision for surgery.

Total knee replacement was recommended in almost all guidelines for the management of the patients with advanced knee OA. Varying degrees of difference in pain relief and improvement in the function and quality of life have been reported. The cumulative rate of revision surgery was estimated to be 10% in several trials.^[87,88] Limitations in function, low mental scores, and comorbidities were reported as negative factors which determined the outcome for patients who underwent TKR.^[89] Total knee replacement was found to be cost-effective with respect to life-long expenses and quality of life and was more expensive and less efficient when performed in small centers, according to a study from the United States.^[90] The SOR was found to be 89.3% (95% CI 84-95).

In summary, an exact cure for knee OA is not possible yet. Preserving and/or improving the structure and function of joints along with providing symptom relief are the main targets in the management of knee OA with various treatment modalities. In this study, scientific evidence was reviewed and with contribution of experts in the field, evidence-based recommendations for the management of knee OA were developed for the first time in our country. The recommendations should be updated regularly according to new evidences and insights. We hope that physicians who are interested in knee OA will benefit from this report in their daily clinical practice.

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