

The management of knee osteoarthritis in elderly: results from a national survey compared to ESCEO guidelines

S. CODAZZA¹, P.E. FERRARA¹, G. GUELI², G. FERRIERO³, G. RONCONI¹,
ON BEHALF OF "KNEE OSTEOARTHRITIS: CPE" STUDY GROUP

¹University Polyclinic Foundation Agostino Gemelli IRCCS, Catholic University of Sacred Heart, Rome, Italy

²Regina Pacis Clinic, San Cataldo, Caltanissetta, Italy

³Istituti Clinici Scientifici Maugeri IRCCS, PRM Unit of Tradate Institute, Tradate, Varese, Italy

Abstract. – OBJECTIVE: Knee osteoarthritis (KOA) is a degenerative and inflammatory disease with a rising incidence and prevalence worldwide. Various therapeutic strategies have been proposed over time, depending on the degrees of severity and usually based on individual clinical practice. However, several European and international scientific societies published guidelines, to provide practical clinical stepwise guidance and to facilitate individualized therapeutic decisions regarding the management of KOA. The aim of this prospective multicentre observational study was to describe the real outpatient territorial management of patients with knee osteoarthritis and to compare it with the ESCEO guidelines, in order to identify operational strategies for delivering patient-centric care.

MATERIALS AND METHODS: The educational project was divided in three modules: the first and the last through webinar; the second held in daily practice. The participants had to register structured observations.

RESULTS: The project has been joined by 155 discussants, and the 2,656 observations collected allowed the understanding of the most common therapeutic approaches for knee osteoarthritis on the Italian territory.

CONCLUSIONS: The educational project proved to be useful for updating on the state of the art of therapeutic management of knee osteoarthritis, and to increase expertise in detecting prevention and treatment strategies according to ESCEO guidelines to apply in the Real-Life context.

Key Words:

Knee osteoarthritis, Conservative treatment, Rehabilitation, Elderly.

Abbreviations

BMI: Body Mass Index; ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; GLFS: Geriatric Locomotive Functional Scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; K-L: Kellgren-Lawrence; KOA: Knee Osteoarthritis; NSAID: Non-Steroidal; OA: Osteoarthritis; SYSADOA: Symptomatic Slow-Acting Drugs for Osteoarthritis; VAS: Visual Analogic Scale.

Introduction

Osteoarthritis (OA) is a degenerative and inflammatory disease of the whole joint¹, comprising cartilage loss and concomitant structural changes of the synovium, periarticular ligaments and subchondral bone².

The incidence of OA is rising, with a number of about 400 million people affected worldwide^{3,4}, and the prevalence is expected to increase due to the aging population and the rising of the obesity rate^{5,6}. Osteoarthritis may involve all joints, but typically affects weight-bearing ones; the knee is the most common articular localization.

Knee osteoarthritis (KOA) represents one of the main causes of pain and disability among subjects aged over 50 years, affecting more than 250 million worldwide⁷, whose degrees of severity and rate of progression varies among patients and within a single joint over time. Factors associated with an increased risk of knee osteoarthritis include older age, female sex, over-

weight or obesity, knee injury, occupational factors and misalignment. Clinical manifestations include pain, stiffness, reduced joint motion and weakness of lower limbs muscles. Long-term consequences can be represented by reduction of physical activity, worsening of motor skills, sleep disorders, fatigue and depression¹.

Knee osteoarthritis progressively invalidates patient's quality of life, increases the risk of all-cause mortality⁸ and determines a substantial rise in public health costs, as a consequence of impaired work productivity and early retirement⁹.

The goals of treatment for knee OA are to reduce the use of painkillers, the impact of disability on patient's quality of life and the early recourse to knee arthroplasty, with a consequent decrease in healthcare resources.

For symptomatic knee OA various therapeutic strategies have been proposed over time, depending on the degrees of severity and in most cases based on common clinical practice or individuals' experience.

However, in the last decades, several European and international scientific societies¹⁰⁻¹² have published recommendations in the form of guidelines, to provide practical clinical stepwise guidance and to facilitate individualized therapeutic decisions regarding the management of knee OA.

The increased use of anti-inflammatory drugs, often not supported by prescriptive appropriateness, and the growing diffusion of joint nutraceuticals and viscosupplementation^{13,14}, have given rise to the need to establish an updated algorithm of available intervention options.

The most accredited guidelines for appropriateness and reliability, based upon application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process¹⁵, are those of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) working group¹². The ESCEO society structured 15 recommendations, 6 of which with strong evidence, in four sequential therapeutic steps, emphasizing the importance of the prioritization of interventions.

The ESCEO working group clarify the therapeutic strategy by indicating the most currently accredited background and rescue pharmacological treatments, strongly recommending the combination of non-pharmacological and pharmacological interventions as the basic principle of the conservative management of KOA.

In this context, the "Real world evidence on the management of patients with knee osteoarthritis" training project was defined and activated, providing a structured observation of the national management methods' of the patient with knee osteoarthritis.

The aim of this prospective multicenter observational study was to describe the real outpatient management of patients with knee osteoarthritis and to compare it with the recommendations of ESCEO guidelines, in order to identify operational strategies for delivering patient-centric care.

Materials and Methods

The educational project "Clinical practice evidence (CPE) for knee osteoarthritis" was included in the context of a national medical training course in blended modality.

The main goals of the educational project were:

- to provide participants with the basic knowledge for the clinical management of patients affected by knee osteoarthritis in the medium and long term;
- to highlight the real diffusion of the clinical issue of knee pain in an outpatients setting, sharing the efficacy and safety of the drugs currently available;
- to detect prevention and treatment models and strategies;
- to allow participants to consolidate the evidences emerged from clinical practice, trying to fill the gap between daily clinical practice and the ESCEO Guidelines for knee osteoarthritis.

The training course was divided in three different modules:

- A first session of Distance Training through webinar, in which the educational course and its goals were introduced and the scientific rationale was shared with learners. Furthermore, the evidence on the pathophysiology of knee osteoarthritis and the current therapeutic strategies were presented; in this preliminary phase, the Activity Book was presented for the collection of patients' data in the real-world. This tool has been analyzed in detail by the tutors, in order to facilitate physicians in collecting data about clinical evaluation and prescribed therapies.

- A daily practice session, which provided the compilation by each participant of the Activity Books, related to the management of the patients affected by knee osteoarthritis. The Activity Book consisted of 40 observations or evaluation sheets, corresponding to 40 patients with knee osteoarthritis. The clinical and functional characteristics and the treatments of the patients with knee osteoarthritis were evaluated in the questionnaires. The main topics recorded were demographic and anamnestic data, radiological degree of KOA according to the Kellgren-Lawrence scale (K-L)¹⁶, pain (VAS), walking deficit and autonomy in the performance of activities of daily living (Geriatric Locomotive Functional Scale - GLFS), local clinical examination data (edema, thermotact, range of motion) and current or previous anti-inflammatory or analgesic drug therapies, use of SYSADOA (symptomatic slow acting drugs for osteoarthritis), intra-articular injections and execution of physical therapy.
- A second session of Distance Training through webinar, in which a collective discussion of overall results was led by tutors, with the comparison of data collected from the real-life practice session and current ESCEO scientific evidence.

The Activity Books were then collected, and a data entry of the information compiled was carried out in order to be able to perform the statistical analysis.

Statistical Analysis

Statistical analysis was performed using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA). Descriptive analysis was performed using standard procedures for the calculation of frequencies measure of average position (arithmetic mean) and dispersion indicators. The

eventual comparison between groups was made by Student's *t*-test with a *p*-level significance < 0.05.

Results

The project has been developed from the 15 October 2020 to 17 May 2021 and has been joined by a total of 155 physicians, consisting of general practitioners and specialists with different clinical and surgical specializations (Physical and Rehabilitation Medicine, Rheumatology, Orthopedics, Geriatrics, Sports Medicine, Anesthesiology).

2,656 clinical observations from patients suffering from knee osteoarthritis were collected. The demographic characteristics of the examined population are shown in Table I.

With regard to the pathognomonic signs and symptoms of KOA, the observation included the recording of the following 8 clinical elements at the level of the affected knee joints: pain, edema, skin condition, creaking, instability, thigh muscle hypotrophy, stiffness and limitation, as shown in Table II.

The goniometric measurement of knee range of motion (ROM) (n = 1,453) showed mean flexion of 92.6 ± 35.8 degrees, and mean extension deficit of 3.84 ± 14.8 degrees.

Regarding the presence of concomitant arthralgias, data showed that pain, as well as at the level of the affected knee, was felt by 58% of interviewed patients also in other joint sites and in particular the contralateral knee, the ipsilateral hip and the rachis.

Out of 2,619 interviews, 694 patients reported having suffered an injury to the painful knee; the remaining 1,925 subjects did not report any traumatic events.

Table III showed the stratification of patients according to Kellgren-Lawrence Scale (K-L) about the radiological severity of knee osteoar-

Table I. Demographic and anthropometric characteristics of the sample.

	Total	Men	Women
Sex number (%)	2,656	1,155 (45.2%)	1,501 (54.8%)
Mean Age (mean \pm standard deviation)	67.2 \pm 11.7	66.8 \pm 12.5	67.6 \pm 11
Weight (kg) (mean \pm standard deviation)	74 \pm 11.6	79.4 \pm 9.7	69.9 \pm 11.2
Mean height (cm) (mean \pm standard deviation)	167.7 \pm 8.3	173.7 \pm 6.8	163.1 \pm 6.2
Body mass index (BMI) (mean \pm standard deviation)	26.4 \pm 3.8	26.4 \pm 3.1	26.4 \pm 4.2

Table II. Signs and symptoms of KOA.

Clinical evaluation: signs and symptoms		
	Present	Absent
Edema (n = 1,426)	78.3%	21.7%
Rubor and calor (n = 843)	47.1%	52.9%
Joint creakings (n = 1,716)	89.5%	10.5%
Instability (n = 1,031)	55.7%	44.3%
Stiffness (n = 1,453)	92.7%	7.3%
Quadriceps hypotrophy (n = 1,434)	81%	19%

thritis, the pain level measured by Visual Analogic Scale (VAS) and the locomotor skills in walking and activities of daily living, that were assessed through Geriatric Locomotive Function Scale (GLFS), expressed in number of patients (n) reported in the questionnaires.

With regard to lifestyle, physical activity was regularly carried out in only 21% of the observations (n = 556). Out of a total of 2,607 subjects, physical activity was performed once a week in 13% of cases, twice a week in 36% of cases and three times a week for 42% of patients. A frequency of 5 times a week or different from the previous ones was found in 47.9% of cases observed. The duration of the single training session ranged from 30 to 120 minutes, with an average of 60 minutes.

Regarding rehabilitation, 2,520 observations were collected. The 53% (n = 1,281) of interviewed patients were undergoing physical therapy at the time of observation or had performed it previously.

The presence of oral pharmacological treatment for osteoarthritis was recorded in 56% of the observations (n = 1,394): 24% of patients

was taking drugs continuously, while 76% used oral therapy limited to the period of acute symptoms.

In Table IV and in Figure 1 the drugs taken by patients before observation (n = 1,149) and after medical prescription (n = 2,299) are described, with a different numerosity based on the data received: the missing data can be traced back to the items not filled in the individual activity books, some of which were therefore incomplete.

The 52% of patients, out of a total of 1,340 observations, underwent intra-articular knee injections.

Discussion

The aim of this prospective multicenter observational study was to describe the real outpatient management of patients with knee osteoarthritis and compare real-life protocols with the indications of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). The ESCEO guidelines are specific for knee osteoarthritis and introduce for the first time the concept of the prioritization of interventions, so as to be considered by our working group a reference point for the discussion of the collected data, also because of the characteristics of appropriateness and reliability, compared to the other existing algorithms^{13,14}.

The six-month research project was joined by 155 general practitioners and specialists throughout the Italian national territory, who collected a total of 2,656 clinical observations from patients suffering from knee osteoarthritis, highlighting a notable adherence and participation to medical training project. During the course, tutors highlighted the real diffusion of the clinical problem of

Table III. Radiological and functional evaluation.

Radiological and functional evaluation (n = number of patients)	
Kellgren-Lawrence Scale (n = 1,518)	
Stage I	7
Stage II	880
Stage III	630
Stage IV	1
Visual Analogic Scale (VAS) (n = 2,073)	
VAS < 4	141
4 ≤ VAS < 7	1,238
7 ≤ VAS ≤ 10	623
Geriatric Locomotive Function Scale (GLFS) (n = 1,634)	
GLFS ≥ 6	1,308
GLFS ≤ 6	326

Table IV. Pharmacological therapy prior and after the clinical observation.

Pharmacological therapy prior and after the clinical observation		
	Prior clinical observation (n = 1,149)	Post clinical observation (n = 2,299)
Paracetamol	11%	7%
NSAIDS	59%	34%
Opioids	5%	4%
SYSADOAs		
- Glucosamine	25%	75%
- Chondroitin Sulfate	2%	2%
- Multiple components	1%	2%
- Missing data	22%	77%
	55%	19%

knee pain in Italy and provided participants with knowledge for the management of knee osteoarthritis in light of the indications of ESCEO guidelines.

The data collection carried out by the 155 physicians during the practice session, with the compilation of the Activity Books, made it possible to evaluate the different treatments for knee osteoarthritis before and after the medical training course, and especially after the explanation of the guidelines.

Collective discussion of the overall results of the observations recorded showed that, with regard to demographic data, the observed population of the present study is in line with

the epidemiology currently known for knee osteoarthritis, in particular for the prevalence of the population over 65 years. Indeed, KOA is the most common osteoarthritis localization, highly prevalent among people aged over 50 years, affecting more than 250 million people worldwide⁷.

Regarding the anthropometric characteristics of the observed population, data showed that the mean value of the Body Mass Index (BMI) was equal to 26.4, with homogeneous distribution between genders, with a condition of overweight in the 52% of patients; about patients' lifestyle, physical activity (about 60 minutes) was carried out weekly in only 21% of cases.

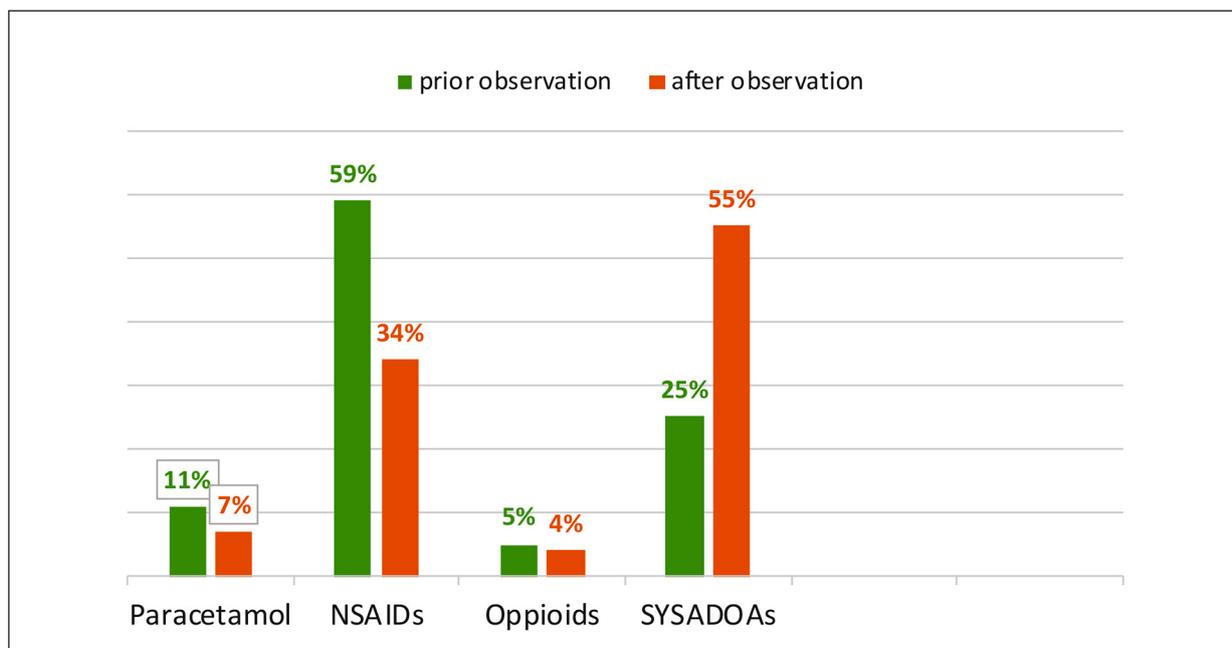


Figure 1. Pharmacological therapy prior and after the clinical observation.

According to literature, obesity¹⁷ and a sedentary lifestyle⁵ are major risk factors for the development of knee osteoarthritis. So, as stated by ESCEO guidelines, the core set of knee osteoarthritis management should be based on patients' information and education to the healthy lifestyle, focused on weight loss if overweight¹⁸ and physical activity, with aerobic, strengthening and resistance exercises¹⁹.

The collection of clinical signs and symptoms (Table I and Table II) are in agreement with the prevalent radiological degree of osteoarthritis according to Kellgren-Lawrence grade recorded in our patients, that corresponds to grade II (definite osteophytes and possible joint space narrowing) and grade III (moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends), and with an algic symptomatology characterized by moderate-severe pain ($5 \leq \text{VAS} < 10$)²⁰.

According to GLFS, pain determines a significant disability for the majority of the sample, as it is greater than the cut off equal to 6 indicated in the literature.

The ESCEO working group clarify the therapeutic strategy for knee osteoarthritis, indicating the most currently accredited background and rescue pharmacological treatments.

Regarding the pharmacological therapy for knee osteoarthritis, our data analysis showed that before observation in the symptomatic phase, the majority of patients took mainly NSAIDs and SYSADOAs and in a smaller percentage paracetamol and opioids. However, after observation, the prescribed therapy showed a clear reduction in the use of NSAIDs and an increase in SYSADOAs; also, a minimal reduction in the prescription of opioids and paracetamol was recorded.

The ESCEO working group discouraged the use of paracetamol as part of knee osteoarthritis background treatment, because of its minimal effect on symptoms²¹ and in light of the increasing evidence of multisystemic adverse events. Conversely, although with a weak recommendation, paracetamol is indicated as short-term rescue analgesic therapy at doses no greater than 3 g/day.

Our data prior observation disagree with ESCEO indications, seeing a predominant use of NSAIDs and paracetamol, and not of SYSADOAs, as recommended. However, the prescribed therapy after observation shows greater adherence to the guidelines, given the reduction in the administration of NSAIDs and paracetamol and the increase in the use of SYSADOAs.

Anti-inflammatory drugs (NSAIDs) can be included in the background therapy, according to ESCEO guidelines, with a strong recommendation only in the topical form, if the patient is still symptomatic after establishing appropriate background therapy with SYSADOAs, and when rescue analgesic therapy with paracetamol has failed.

Instead, selective or non-selective oral NSAIDs, according to ESCEO experts, must constitute the advanced pharmacological treatment, and must be administrated in intermittent or prolonged cycles in the subjects with persistent symptoms, based on the single patient risk profile.

In the case of contraindications to NSAIDs, or if the patient is still symptomatic despite use of NSAIDs, intra-articular injections of hyaluronic acid and corticosteroids may be taken into account, although with a weak ESCEO recommendation, as alternative therapeutic strategy, with a more favorable safety profile, especially for older patients. The data deriving from our observations show that 52% of patients underwent infiltrative therapy during or after oral treatment, in the most severe cases or in those non-responsive to drug therapy.

About short-term weak opioids, our data showed that they have been used before and after clinical observation, by a small percentage of patients as the first pharmacological attempt, instead of using them in the end-stage disease management before surgical, as recommended by ESCEO guidelines, which also clarifies strong opioids use when total joint replacement is contraindicated.

The strongly recommended approach from ESCEO group is to establish long-term background therapy with crystal-line glucosamine sulfate (pCGS), since it represents the only one for which it has been demonstrated high glucosamine bio-availability and adequate plasma concentration in humans²²⁻²⁵. From the observations collected instead, an almost insignificant percentage (2%) of glucosamine emerges both in the therapy before the observation and in the prescribed therapy. ESCEO guidelines indicate the chondroitin sulfate as an alternative to pCGS, but not in association, because the combination of glucosamine and chondroitin sulfate has scarce evidence and so it is weakly recommended.

However, unlike the ESCEO indications that affords a strong recommendation to the use of only crystalline glucosamine sulfate (pGCS), our data show the use of SYSADOAs with more

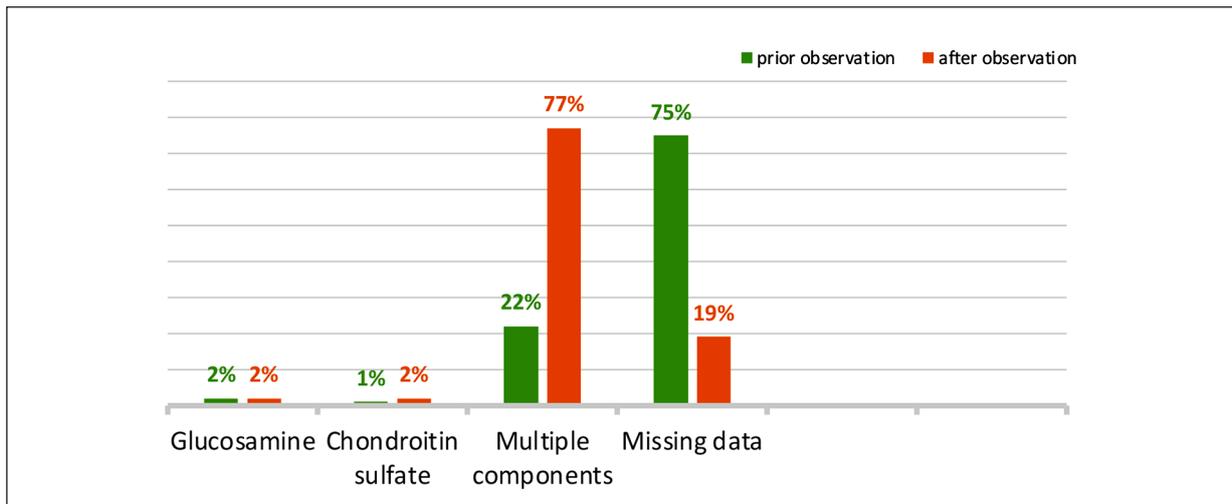


Figure 2. Symptomatic Slow-Acting Drugs for Osteoarthritis (SYSADOAs) prior and after the clinical observation.

components in most of the observations both before and especially after clinical evaluation, with a doubling in use in the prescribed therapy, as shown in Figure 2.

Conclusions

The goals of treatment for symptomatic knee OA are to relieve symptoms and to slow cartilage degeneration, with a consequent improvement of quality of life and healthcare costs' reduction. The European working group of ESCEO provides the most accredited and specific guidelines in the form of step algorithm, to provide practical clinical guidance and to facilitate individualized therapeutic decisions.

This on-field training project has been very useful for understanding the real situation of therapeutic management of the different degrees of severity of knee osteoarthritis. The collective discussion allowed the participants to update themselves on the state of the art of therapeutic management of knee osteoarthritis, and to increase expertise in detecting prevention and treatment strategies to apply in the Real-Life context.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethics Approval

Not applicable.

Data Availability

Database available upon request.

Authors' Contribution

All the authors equally contributed, read and approved the final manuscript. SC: contribution in acquisition, analysis of data and drafted work. PEF: contribution in conception acquisition, analysis of data and drafted paper. GG: contribution in acquisition of data and revision of paper. GF: contribution in revision of paper. GR: contribution in conception, interpretation and revision of paper.

Funding

This research was supported by FENIXPHARMA.

References

- 1) Sharma L, Osteoarthritis of the Knee. *N Engl J Med* 2021; 384: 51-59.
- 2) Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. *Ann Phys Rehabil Med* 2016; 59: 333-339.
- 3) Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: Epidemiology and therapy. *Osteoarthr Cartil* 2020; 28: 242-248.
- 4) Mokdad AH, Balletros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ, Kasaeian A, Werdecker A, Carter A, Zipkin B, Sartorius B, Serdar B, Sykes BL, Tro-

- eger C, Fitzmaurice C, Rehm CD, Santomauro D, Kim D, Colombara D, Schwebel DC, Tsoi D, Kolte D, Nsoesie E, Nichols E, Oren E, Charlson FJ, Patton GC, Roth GA, Hosgood HD, Whiteford HA, Kyu H, Erskine HE, Huang H, Martopullo I, Singh JA, Nachega JB, Sanabria JR, Abbas K, Ong K, Tabb K, Krohn KJ, Cornaby L, Degenhardt L, Moses M, Farvid M, Griswold M, Criqui M, Bell M, Nguyen M, Wallin M, Mirarefin M, Qorbani M, Younis M, Fullman N, Liu P, Briant P, Gona P, Havmoller R, Leung R, Kimokoti R, Bazargan-Hejazi S, Hay SI, Yadgir S, Biryukov S, Vollset SE, Alam T, Frank T, Farid T, Miller T, Vos T, Bärnighausen T, Gebrehiwot TT, Yano Y, Al-Aly Z, Mehari A, Handal A, Kandel A, Anderson B, Biroscak B, Mozaffarian D, Dorsey ER, Ding EL, Park E-K, Wagner G, Hu G, Chen H, Sunshine JE, Khubchandani J, Leasher J, Leung J, Salomon J, Unutzer J, Cahill L, Cooper L, Horino M, Brauer M, Breitborde N, Hotez P, Topor-Madry R, Soneji S, Stranges S, James S, Amrock S, Jayaraman S, Patel T, Akinyemiju T, Skirbekk V, Kinfu Y, Bhutta Z, Jonas JB, Murray CJL. US Burden of Disease Collaborators. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA* 2018; 319: 1444-1472.
- 5) Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011; 377: 2115-2126.
 - 6) Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *E Clinical Medicine* 2020; 29-30: 100587.
 - 7) Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Badour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel P, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipschultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De León FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shiva-koti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whitford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2163-2196.
 - 8) Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis:

- population-based cohort study. *BMJ* 2011; 342: d1165.
- 9) Hermans J, Koopmanschap MA, Sita MA, Bierma-Zeinstra SM, van Linge JH, Verhaar JA, Reijman M, Burdorf A. Productivity costs and medical costs among working patients with knee osteoarthritis. *Arthritis Care Res (Hoboken)* 2012; 64: 853-861.
 - 10) Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzig E, Kwok CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, Di Renzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Aakash Shah A, Shmigel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis & Rheumatol* 2020; 72: 220-233.
 - 11) Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojjan T, Underwood M, Mc Alindon TE. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019; 27: 1578-1589.
 - 12) Bruyère O, Honvo G, Veronese N, Arden N.K, Brancof J, Curtise E.M, Al-Daghrig N.M, Herero-Beaumont G, Martel-Pelletieri J, Pelletieri J-P, Rannouj F, Rizzolli R, Rothl R, Uebelhartm D, Cooperb C, Reginster J-Y. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). *Semin Arthritis and Rheuma* 2019; 49: 337-350.
 - 13) Liu X, Machado GC, Eyles JP, Ravi V, Hunter DJ. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med Actions* 2018; 52: 167-175.
 - 14) Peck J, Slovek A, Miro P, Vij N, Traube B, Lee C, Berger AA, Kassem H, Kaye AD, Sherman WF, Abd-Elsayed A. A Comprehensive Review of Viscosupplementation in Osteoarthritis of the Knee. *Orthop Rev* 2021; 13: 25549.
 - 15) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924.
 - 16) Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957; 16: 494-502.
 - 17) Misra D, Fielding RA, Felson DT, Niu J, Brown C, Nevitt M, Lewis CE, Torner J, Neogi T. Risk of knee osteoarthritis with obesity, sarcopenic obesity and sarcopenia. *Arthritis Rheumatol* 2019; 71: 232-237.
 - 18) Messier SP, Resnik AE, Beavers DP, Mihalko SL, Miller GD, Nicklas BJ, deVita P, Hunter DJ, Lyles MF, Eckstein F, Guermazi A, Loeser RF. Intentional weight loss in overweight and obese patients with knee osteoarthritis: is more better? *Arthritis Care Res (Hoboken)* 2018; 70: 1569-1575.
 - 19) Gay C, Chabaud A, Guilley E, Coudeyre E. Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. System literature review. *Ann Phys Rehabil Med* 2016; 59: 174-183.
 - 20) Pongsakonpruttikul N, Anghthong C, Kittichai V, Chuwongin S, Puengpipattrakul P, Thongpat P, Boonsang S, Tongloy T. Artificial intelligence assistance in radiographic detection and classification of knee osteoarthritis and its severity: a cross-sectional diagnostic study. *Eur Rev Med Pharmacol Sci* 2022; 26: 1549-1558
 - 21) Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med* 2015; 162: 46-54.
 - 22) Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2009: CD002946.
 - 23) Bruyere O, Altman RD, Reginster J-Y. Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: evidence from real-life setting trials and surveys. *Semin Arthritis Rheum* 2016; 45: S12-S17.
 - 24) Kucharz EJ, Kovalenko V, Szanto S, Bruyere O, Cooper C, Reginster JY. A review of glucosamine for knee osteoarthritis: why patented crystalline glucosamine sulfate should be differentiated from other glucosamines to maximize clinical outcomes. *Curr Med Res Opin* 2016; 32: 997-1004.
 - 25) Sevimli R, Erenler AS, Karabulut AB, Akpolat N, H Geçkil H. Microbial chondroitin sulfate in experimental knee osteoarthritis model investigation of chondroprotective effect. *Eur Rev Med Pharmacol Sci* 2021; 25: 5402-5411.