



## DİZ OSTEOARTRİTİNDE FARMAKOLOJİK VE NONFARMAKOLOJİK TEDAVİ YÖNTEMLERİ

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### GİRİŞ

Osteoartrit (OA), eklemi oluşturan kıkırdak ve periartiküler yapıların etkilendiği dejeneratif bir hastalıktır. Aynı zamanda en sık görülen artrit formu olup, kıkırdak yıkımı, kemik yeniden şekillenmesi, osteofit oluşumu ve sinovyal inflamasyon dahil olmak üzere tüm eklemi içeren, ağrı, sertlik, şişme ve normal eklem fonksiyonunun kaybı ile karakterizedir. OA tedavisinde kullanılan konvansiyonel ve alternatif tedavi yöntemleri Tablo-1’ de nonfarmakolojik- farmakolojik olarak kategorize edilmiştir.

**Tablo 1. Diz osteoartrisinde farmakolojik ve nonfarmakolojik tedavi yöntemleri**

Nonfarmakolojik Tedavi Yöntemleri	Farmakolojik Tedavi Yöntemleri
Hasta eğitimi ve kilo vermenin önerilmesi	Asetaminofen
Ortezler	Nonsteroid Anti-İnflamatuar İlaçlar (Nsaid)
Yürüme yardımcı cihazlar	Duloksetin
Egzersiz	Kapsaisin
Fizik tedavi ajanları	Opioid analjezikler
Manuel terapi, masaj	Besin takviyeleri
Tai Chi, Yoga	Glukozamin ve kondroitin sülfat
Bilişsel davranışçı tedavi	Diaserein
Akupunktur	Eklem içi enjeksiyon tedavileri
Kinezyobantlama	Yeni tedavi yöntemleri

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**Güncel kılavuzlara göre;** ACR, TNF alfa, IL-1 inhibitörleri, metotreksat ve hidroklorokini önermez (güçlü karşı öneri). Analjezik etkisi olabileceğinden kolşisini koşullu karşı öneri olarak belirtmiştir. Ayrıca botulinum nörotoksin eklem içi uygulamasının OA' da herhangi bir etkisi görülmediğinden koşullu karşı öneri olarak belirtilmiştir (7). Diğer yeni tedaviler kılavuzlarda yer almaktadır.

## KAYNAKLAR

1. Gómez R, Conde J, Scotece M, et al. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nature Reviews Rheumatology*. 2011;7(9):528-36.
2. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *Jama*. 2013;310(12):1263-73.
3. Riddle DL, Stratford PW. Body weight changes and corresponding changes in pain and function in persons with symptomatic knee osteoarthritis: a cohort study. *Arthritis care & research*. 2013;65(1):15-22.
4. Tuncer T, Cay FH, Altan L, et al. 2017 update of the Turkish League Against Rheumatism (TLAR) evidence-based recommendations for the management of knee osteoarthritis. *Rheumatology international*. 2018;38(8):1315-31.
5. Bannuru RR, Osani M, Vaysbrot E, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis and cartilage*. 2019;27(11):1578-89.
6. Geenen R, Overman CL, Christensen R, et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Annals of the rheumatic diseases*. 2018;77(6):797-807.
7. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis & Rheumatology*. 2020;72(2):220-33.
8. Bruyère O, Honvo G, Veronese N, et al., editors. 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). *Seminars in arthritis and rheumatism*; 2019: Elsevier.
9. Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. *Caspian journal of internal medicine*. 2011;2(2):205.
10. Chehab EF, Favre J, Erhart-Hledik JC, et al. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthritis and cartilage*. 2014;22(11):1833-9.

11. Mølgaard CM, Graven-Nielsen T, Simonsen O, et al. Potential interaction of experimental knee pain and laterally wedged insoles for knee off-loading during walking. *Clinical Biomechanics*. 2014;29(8):848-54.
12. Kerrigan DC, Lelas JL, Goggins J, et al. Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. *Archives of physical medicine and rehabilitation*. 2002;83(7):889-93.
13. Moyer RF, Birmingham TB, Dombroski CE, et al. Combined effects of a valgus knee brace and lateral wedge foot orthotic on the external knee adduction moment in patients with varus gonarthrosis. *Archives of physical medicine and rehabilitation*. 2013;94(1):103-12.
14. Khosravi M, Arazpour M, Vaziri AS. An evaluation of the use of a lateral wedged insole and a valgus knee brace in combination in subjects with medial compartment knee osteoarthritis (OA). *Assistive Technology*. 2019.
15. Rodrigues PT, Ferreira AF, Pereira RM, et al. Effectiveness of medial-wedge insole treatment for valgus knee osteoarthritis. *Arthritis Care & Research: Official Journal of the American College of Rheumatology*. 2008;59(5):603-8.
16. Khosravi M, Babae T, Daryabor A, et al. Effect of knee braces and insoles on clinical outcomes of individuals with medial knee osteoarthritis: A systematic review and meta-analysis. *Assistive Technology*. 2021:1-17.
17. Callaghan MJ, Parkes MJ, Felson DT. The effect of knee braces on quadriceps strength and inhibition in subjects with patellofemoral osteoarthritis. *Journal of orthopaedic & sports physical therapy*. 2016;46(1):19-25.
18. McGibbon CA, Brandon S, Bishop EL, et al. Biomechanical Study of a Tricompartamental Unloader Brace for Patellofemoral or Multicompartamental Knee Osteoarthritis. *Frontiers in bioengineering and biotechnology*. 2021;8:1528.
19. Gohal C, Shanmugaraj A, Tate P, et al. Effectiveness of valgus offloading knee braces in the treatment of medial compartment knee osteoarthritis: a systematic review. *Sports health*. 2018;10(6):500-14.
20. Van Ginckel A, Hinman R, Wrigley T, et al. Effect of cane use on bone marrow lesion volume in people with medial tibiofemoral knee osteoarthritis: randomized clinical trial. *Osteoarthritis and cartilage*. 2019;27(9):1324-38.
21. Karasavvidis T, Hirschmann MT, Kort NP, et al. Home-based management of knee osteoarthritis during COVID-19 pandemic: literature review and evidence-based recommendations. *Journal of experimental orthopaedics*. 2020;7(1):1-7.
22. Zhang W, Nuki G, Moskowitz R, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and cartilage*. 2010;18(4):476-99.
23. Goh S-L, Persson MS, Stocks J, et al. Relative efficacy of different exercises for pain, function, performance and quality of life in knee and hip osteoarthritis: systematic review and network meta-analysis. *Sports Medicine*. 2019;49(5):743-61.

24. Hunter DJ, Harvey W, Gross KD, et al. A randomized trial of patellofemoral bracing for treatment of patellofemoral osteoarthritis. *Osteoarthritis and cartilage*. 2011;19(7):792-800.
25. Timmins KA, Leech RD, Batt ME, et al. Running and knee osteoarthritis: a systematic review and meta-analysis. *The American journal of sports medicine*. 2017;45(6):1447-57.
26. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the US bone and joint initiative. *Seminars in arthritis and rheumatism*; 2014: Elsevier.
27. Bartels EM, Juhl CB, Christensen R, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database of Systematic Reviews*. 2016(3).
28. Newberry SJ, FitzGerald J, SooHoo NF, et al. Treatment of osteoarthritis of the knee: an update review. *Europe PMC*. 2017.
29. Chen L-X, Zhou Z-R, Li Y-L, et al. Transcutaneous electrical nerve stimulation in patients with knee osteoarthritis. *The Clinical journal of pain*. 2016;32(2):146-54.
30. Wu Y, Zhu S, Lv Z, et al. Effects of therapeutic ultrasound for knee osteoarthritis: a systematic review and meta-analysis. *Clinical rehabilitation*. 2019;33(12):1863-75.
31. Zhang C, Xie Y, Luo X, et al. Effects of therapeutic ultrasound on pain, physical functions and safety outcomes in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clinical Rehabilitation*. 2016;30(10):960-71.
32. Altaş EU, Demirdal Ü. The effect of physical therapy and rehabilitation modalities on sleep quality in patients with primary knee osteoarthritis: A single-blind, prospective, randomized-controlled study. *Turkish journal of physical medicine and rehabilitation*. 2020;66(1):73.
33. Devrimsel G, Metin Y, Serdaroglu Beyazal M. Short-term effects of neuromuscular electrical stimulation and ultrasound therapies on muscle architecture and functional capacity in knee osteoarthritis: a randomized study. *Clinical rehabilitation*. 2019;33(3):418-27.
34. Kan L, Zhang J, Yang Y, et al. The effects of yoga on pain, mobility, and quality of life in patients with knee osteoarthritis: a systematic review. *Evidence-Based Complementary and Alternative Medicine*. 2016;2016.
35. Mat S, Tan MP, Kamaruzzaman SB, et al. Physical therapies for improving balance and reducing falls risk in osteoarthritis of the knee: a systematic review. *Age and ageing*. 2014;44(1):16-24.
36. Pitsillides A, Stasinopoulos D, Giannakou K. The effects of cognitive behavioural therapy delivered by physical therapists in knee osteoarthritis pain: A systematic review and meta-analysis of randomized controlled trials. *Journal of bodywork and movement therapies*. 2021;25:157-64.
37. Corbett M, Rice S, Madurasinghe V, et al. Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. *Osteoarthritis and cartilage*. 2013;21(9):1290-8.

38. Manyanga T, Froese M, Zarychanski R, et al. Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis. *BMC complementary and alternative medicine*. 2014;14(1):1-9.
39. Lin X, Huang K, Zhu G, et al. The effects of acupuncture on chronic knee pain due to osteoarthritis: a meta-analysis. *Journal of Bone and Joint Surgery*. 2016;98(18):1578-85.
40. Ayas A. Diz osteoartritli hastalarda dizlik ve bantlamanın denge ve fonksiyonellik üzerine etkinliğinin karşılaştırılması: *Sağlık Bilimleri Enstitüsü*; 2018.
41. Ye W, Jia C, Jiang J, et al. Effectiveness of elastic taping in patients with knee osteoarthritis: A systematic review and meta-analysis. *American journal of physical medicine & rehabilitation*. 2020;99(6):495-503.
42. Lin C-H, Lee M, Lu K-Y, et al. Comparative effects of combined physical therapy with Kinesio taping and physical therapy in patients with knee osteoarthritis: a systematic review and meta-analysis. *Clinical Rehabilitation*. 2020;34(8):1014-27.
43. Botting RM. Mechanism of action of acetaminophen: is there a cyclooxygenase 3? *Clinical Infectious Diseases*. 2000;31(Supplement\_5):S202-S10.
44. Beyazova M, Kutsal YG. Fiziksel Tıp ve Rehabilitasyon 2016. 2081 p.
45. Hochberg M. Romatoloji. Hochberg MC, editor 2011.
46. Barthel HR, Axford-Gatley RA. Topical nonsteroidal anti-inflammatory drugs for osteoarthritis. *Postgraduate medicine*. 2010;122(6):98-106.
47. Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *British journal of anaesthesia*. 2011;107(4):490-502.
48. Rodriguez-Merchan EC. Topical therapies for knee osteoarthritis. *Postgraduate Medicine*. 2018;130(7):607-12.
49. Sharma L. Osteoarthritis C. treatment. Primer on the Rheumatic Diseases: Thirteenth Edition: *Springer New York*; 2008. p. 235-40.
50. Wang Z, Jones G, Winzenberg T, et al. Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion-Synovitis of Knee Osteoarthritis: A Randomized Trial. *Annals of Internal Medicine*. 2020;173(11):861-9.
51. Henrotin Y, Clutterbuck A, Allaway D, et al. Biological actions of curcumin on articular chondrocytes. *Osteoarthritis and cartilage*. 2010;18(2):141-9.
52. Mathy-Hartert M, Jacquemond-Collet I, Priem F, et al. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflammation Research*. 2009;58(12):899-908.
53. Akinyemi I. Tumeric or curcumin and the treatment of knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials: *NTNU*; 2021.
54. Hsiao A-F, Lien Y-C, Tzeng I-S, Liu C-T, Chou S-H, Horng Y-S. The Efficacy of High-and Low-dose Curcumin in Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Complementary therapies in medicine*. 2021:102775.
55. Rahimnia A-R, Panahi Y, Alishiri G, et al. Impact of supplementation with curcuminoids on systemic inflammation in patients with knee osteoarthritis: findings from a randomized double-blind placebo-controlled trial. *Drug research*. 2015;65(10):521-5.

56. Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*. *Clinical pharmacokinetics*. 2011;50(6):349-69.
57. Sengupta K, Kolla JN, Krishnaraju AV, et al. Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: a novel *Boswellia serrata* extract. *Molecular and cellular biochemistry*. 2011;354(1):189-97.
58. Yu G, Xiang W, Zhang T, et al. Effectiveness of *Boswellia* and *Boswellia* extract for osteoarthritis patients: a systematic review and meta-analysis. *BMC Complementary Medicine and Therapies*. 2020;20(1):1-16.
59. Butawan M, Benjamin RL, Bloomer RJ. Methylsulfonylmethane: applications and safety of a novel dietary supplement. *Nutrients*. 2017;9(3):290.
60. Richmond VL. Incorporation of methylsulfonylmethane sulfur into guinea pig serum proteins. *Life sciences*. 1986;39(3):263-8.
61. Ahn H, Kim J, Lee M-J, et al. Methylsulfonylmethane inhibits NLRP3 inflammasome activation. *Cytokine*. 2015;71(2):223-31.
62. Notarnicola A, Maccagnano G, Moretti L, et al. Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial. *International journal of immunopathology and pharmacology*. 2016;29(1):140-6.
63. Sharma S, Sahu D, Das HR, et al. Amelioration of collagen-induced arthritis by *Salix nigra* bark extract via suppression of pro-inflammatory cytokines and oxidative stress. *Food and chemical toxicology*. 2011;49(12):3395-406.
64. Bonaterra G, Heinrich E, Kelber O, et al. Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv®) in LPS-activated human monocytes and differentiated macrophages. *Phytomedicine*. 2010;17(14):1106-13.
65. Shara M, Stohs SJ. Efficacy and safety of white willow bark (*Salix alba*) extracts. *Phytotherapy Research*. 2015;29(8):1112-6.
66. Rohdewald PJ. Review on sustained relief of osteoarthritis symptoms with a proprietary extract from pine bark, Pycnogenol. *Journal of medicinal food*. 2018;21(1):1-4.
67. Robertson NU, Schoonees A, Brand A, Visser J. Pine bark (*Pinus* spp.) extract for treating chronic disorders. *Cochrane Database of Systematic Reviews*. 2020(9).
68. Christiansen BA, Bhatti S, Goudarzi R, et al. Management of osteoarthritis with avocado/soybean unsaponifiables. *Cartilage*. 2015;6(1):30-44.
69. Christensen R, Bartels E, Astrup A, Bliddal H. Symptomatic efficacy of avocado- soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis and cartilage*. 2008;16(4):399-408.
70. Simental-Mendía M, Sánchez-García A, Acosta-Olivo CA, et al. Efficacy and safety of avocado-soybean unsaponifiables for the treatment of hip and knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials. *International journal of rheumatic diseases*. 2019;22(9):1607-15.
71. Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. *Nutrition journal*. 2015;15(1):1-15.

72. Hewlings S, Kalman D, Schneider LV. A randomized, double-blind, placebo-controlled, prospective clinical trial evaluating water-soluble chicken eggshell membrane for improvement in joint health in adults with knee osteoarthritis. *Journal of medicinal food*. 2019;22(9):875-84.
73. Bruyere O, Pavelka K, Rovati LC, et al. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. *Menopause*. 2004;11(2):138-43.
74. Truong TTT, Lim JM, Cho H-R, et al. A double-blind, randomized controlled 12-week follow-up trial to evaluate the efficacy and safety of polycan in combination with glucosamine for the treatment of knee osteoarthritis. *Evidence-Based Complementary and Alternative Medicine*. 2019;2019.
75. Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis & Rheumatism*. 2005;52(3):779-86.
76. Simental-Mendía M, Sánchez-García A, Vilchez-Cavazos F, et al. Effect of glucosamine and chondroitin sulfate in symptomatic knee osteoarthritis: a systematic review and meta-analysis of randomized placebo-controlled trials. *Rheumatol Int*. 2018;38(8):1413-28.
77. Zhu X, Wu D, Sang L, et al. Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: a network meta-analysis. *Clinical and experimental rheumatology*. 2018;36(4):595-602.
78. Pavelká K, Gatterová J, Olejarová M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Archives of internal medicine*. 2002;162(18):2113-23.
79. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: The study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 2009;60(2):524-33.
80. Henrotin Y, Marty M, Mobasher A. What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? *Maturitas*. 2014;78(3):184-7.
81. Pujol J-P, Chadjichristos C, Legendre F, Baugé C, Beauchef G, Andriamanalijaona R, et al. Interleukin-1 and transforming growth factor- $\beta$  1 as crucial factors in osteoarthritic cartilage metabolism. *Connective tissue research*. 2008;49(3-4):293-7.
82. Boileau C, Tat SK, Pelletier J-P, et al. Diacerein inhibits the synthesis of resorptive enzymes and reduces osteoclastic differentiation/survival in osteoarthritic subchondral bone: a possible mechanism for a protective effect against subchondral bone remodelling. *Arthritis research & therapy*. 2008;10(3):1-10.
83. Panova E, Jones G. Benefit–risk assessment of diacerein in the treatment of osteoarthritis. *Drug safety*. 2015;38(3):245-52.
84. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. *Cochrane Database of Systematic Reviews*. 2015(10).

85. Cook CS, Smith PA. Clinical update: why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. *Current reviews in musculoskeletal medicine*. 2018;11(4):583-92.
86. Levy DM, Petersen KA, Vaught MS, et al. Injections for knee osteoarthritis: corticosteroids, viscosupplementation, platelet-rich plasma, and autologous stem cells. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*. 2018;34(5):1730-43.
87. MacMahon PJ, Eustace SJ, Kavanagh EC. Injectable corticosteroid and local anesthetic preparations: a review for radiologists. *Radiology*. 2009;252(3):647-61.
88. Jordan K, Arden N, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the rheumatic diseases*. 2003;62(12):1145-55.
89. Altman R, Hackel J, Niazi F, et al. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: a systematic review. *Seminars in arthritis and rheumatism*; 2018: Elsevier.
90. Ray TR. Using viscosupplementation to treat knee osteoarthritis. *The Physician and sportsmedicine*. 2013;41(4):16-24.
91. Yıldız C, Özgürtaş T. Trombositten zengin plazma.
92. Maynard D, Heijnen H, Horne M, et al. Proteomic analysis of platelet  $\alpha$ -granules using mass spectrometry. *Journal of thrombosis and haemostasis*. 2007;5(9):1945-55.
93. Rendu F, Brohard-Bohn B. The platelet release reaction: granules' constituents, secretion and functions. *Platelets*. 2001;12(5):261-73.
94. van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. *The American journal of sports medicine*. 2011;39(11):2362-70.
95. Kabiri A, Esfandiari E, Esmaeili A, et al. Platelet-rich plasma application in chondrogenesis. *Advanced biomedical research*. 2014;3.
96. Bocci VA. Tropospheric ozone toxicity vs. usefulness of ozone therapy. *Archives of medical research*. 2007;38(2):265-7.
97. Yeprem L, Uluşan N. Ozon Tedavisinde Doktorun El Kitabı L. Y, N. U, editors. Antaya: Kongre Kitabevi 2019.
98. Bocci V, Valacchi G, Rossi R, et al. Studies on the biological effects of ozone: 9. Effects of ozone on human platelets. *Platelets*. 1999;10(2-3):110-6.
99. Emadedin M, Aghdami N, Taghiyar L, et al. Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. *Archives of Iranian medicine*. 2012;15(7):0-.
100. Emadedin M, Liastani MG, Fazeli R, et al. Long-term follow-up of intra-articular injection of autologous mesenchymal stem cells in patients with knee, ankle, or hip osteoarthritis. *Archives of Iranian medicine*. 2015;18(6):0-.
101. Al-Najar M, Khalil H, Al-Ajlouni J, et al. Intra-articular injection of expanded autologous bone marrow mesenchymal cells in moderate and severe knee osteo-



- oarthritis is safe: a phase I/II study. *Journal of orthopaedic surgery and research*. 2017;12(1):1-6.
102. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). *Journal of translational medicine*. 2016;14(1):1-9.
  103. Vega A, Martín-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. *Transplantation*. 2015;99(8):1681-90.
  104. Centeno CJ, Al-Sayegh H, Bashir J, et al. A dose response analysis of a specific bone marrow concentrate treatment protocol for knee osteoarthritis. *BMC musculoskeletal disorders*. 2015;16(1):1-8.
  105. Kim J-D, Lee GW, Jung GH, et al. Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. *European Journal of Orthopaedic Surgery & Traumatology*. 2014;24(8):1505-11.
  106. Jo CH, Lee YG, Shin WH et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem cells*. 2014;32(5):1254-66.
  107. Wang J, Liang J, Yao J, et al. Meta-analysis of clinical trials focusing on hypertonic dextrose prolotherapy (HDP) for knee osteoarthritis. *Aging clinical and experimental research*. 2021.
  108. Schmelz M, Mantyh P, Malfait, et al. Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety. *Pain*. 2019;160(10):2210.
  109. Hochberg MC, Carrino JA, Schnitzer TJ, et al. Long-Term Safety and Efficacy of Subcutaneous Tanezumab Versus Nonsteroidal Antiinflammatory Drugs for Hip or Knee Osteoarthritis: A Randomized Trial. *Arthritis & Rheumatology*. 2021.
  110. Cao P, Li Y, Tang Y, et al. Pharmacotherapy for knee osteoarthritis: Current and emerging therapies. *Expert opinion on pharmacotherapy*. 2020;21(7):797-809.
  111. Hochberg MC, Guermazi A, Guehring H, et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *Jama*. 2019;322(14):1360-70.
  112. Roemer FW, Aydemir A, Lohmander S, et al. Structural effects of sprifermin in knee osteoarthritis: a post-hoc analysis on cartilage and non-cartilaginous tissue alterations in a randomized controlled trial. *BMC musculoskeletal disorders*. 2016;17(1):1-7.