

Do Mechanoreceptors bear significance in osteoarthritis knee patients?

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Abstract:

Prevalence rate of osteoarthritis patients older than 40 years in India and across globe has emerged as a concern for which treatment has become absolute for survival. Empirical evidences and evidence based practices in the last few decades reveals that significant attempts have been made to treat and manage osteoarthritis. These

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interventions used in treating osteoarthritis have adverse effects as well as, burden of treatment cost due to long duration of treatment. Such interventions though have noticeable short term effects but their long term effects are rarely studied due to a number of problems and issues involved in conducting longitudinal studies. Therefore, the need is felt for increasing efficiency in treatment of osteoarthritis patients, where the present researcher attempted to analyze the role of mechanoreceptors in osteoarthritis knee patients with regard to Proprioceptive Neuromuscular Facilitation (PNF) stretching and Passive Joint Mobilization (PJM). There have been studies on PNF stretching and PJM in India as well as in western world. However these studies were limited by smaller sample size . Hence authors are currently conducting a study with larger sample size to assess effectiveness of PNF stretching and PJM in osteoarthritis of knee joint patients in a tertiary care superspeciality hospital in India. In the context of the designed study, attempt has been made to discuss the conceptual framework on osteoarthritis patients in relation to PNF stretching and PJM in the form of present article as a scholarly contribution.

Key words: Mechanoreceptors, osteoarthritis knee patients

INTRODUCTION

Osteoarthritis is one of the most prevalent degenerative condition which leads to pain and disability among adults (Allen KD et al¹). It often affects hip, knees, feet, shoulder, hands and spine . Although Osteoarthritis is age related disease , the risk factors associated with it are obesity, sedentary life style, hereditary, low bone density, job related injury, trauma, and gender (Haq I et al²). As part of the Global Burden of Disease 2010 study, a systematic review reported that the global age-standardized prevalence of knee osteoarthritis was 3.8% (Allen KD et al¹). According to the United Nations, by 2050 people aged over 60 will account for osteoarthritis more than 20% of the world's population.

Prevalence of osteoarthritis is 22% to 39% in India. Osteoarthritis causes pain and affects mobility of joints (Chandra Prakash Pal et al³). It is evident that osteoarthritis will be a major concern in future as a result of increasing number of aging population due to improved human life expectancy. Despite many available treatment options there is scope for treatments which improves symptoms with minimal or negligible side effects.

Evidence based practices in the treatment and management of osteoarthritis can be broadly classified into pharmacological and non pharmacological treatment. Pharmacological treatment includes acetaminophen, Non steroidal anti inflammatory drugs (NSAIDs), Opioids, Intra articular injections, Glucosamine sulfate and chondroitin sulfate. Non pharmacological treatment includes hydrotherapy, massage therapy, thermotherapy, electrotherapy, Manual therapy and surgery (Yusuf E⁴). Each of these treatments are discussed below with its current evidence based practices .

THEORETICAL AND CONCEPTUAL FRAMEWORK

Significance of mechanoreceptors in reducing pain and increasing range of motion (ROM) in the primary reference that has been influencing clinical practices and have been mentioned in scholarly contributions in medical sciences in terms of theoretical constructs. Four major theoretical propositions in human physiology supports in easing pain and increasing ROM of joints are Autogenic Inhibition, Reciprocal Inhibition, Stress relaxation (Kindle KB et al⁵) and pain gate theory (Ronald Melzack and Patrick D. Wall⁶).

Autogenic Inhibition

Autogenic Inhibition is the self inhibition of contracted muscle, occurs due to activation of Golgi tendon organ. When a muscle undergoes isometric contraction the tension in muscle increases

leading to activation of Golgi tendon organ, which in turn through afferent nerve fibers reaches the spinal cord. In spinal cord these fibers inhibit the alpha motor neurons of the target muscle via activating inhibitory interneurons. Simultaneously alpha motor neurons of antagonist muscle to target muscle gets activated by inhibiting the inhibitory interneurons. There by the target muscle relaxes and antagonist muscle contracts (Kindle KB et al⁵).

Reciprocal Inhibition

Reciprocal Inhibition occurs when antagonist to target muscle is contracted. As antagonist muscle contracts its neural activity gets increased and afferent nerve fibers reaches spinal cord. In spinal cord these fibers stimulate inhibitory inter neurons, which in turn inhibit firing of alpha motor neuron of target muscle. Therefore target muscle is relaxed (i.e) neural activity and proprioceptors activity is minimized (Kindle KB et al⁵).

Stress Relaxation

When a muscle is under prolonged stress, the Musculotendinous Unit (MTU) of muscle due to their viscoelastic property undergoes a phenomenon known as stress relaxation. So viscous material loses its ability to overcome the stretch, MTU slowly increase in length known as creep of MTU, which resulted in increase in length of muscle and joint ROM (Kindle KB et al⁵).

Pain gate theory

When receptors of two different sensations (pain and pressure) are stimulated pain gate theory comes into existence. Mechanoreceptors which is connected to large diameter myelinated (type A nerve fibers) carries impulse faster than pain receptors which is connected to small diameter unmyelinated nerve fibers (type C nerve fibers). When both receptors are stimulated simultaneously type A fibers carries

nerve impulse faster to spinal cord than type C fibers. In spinal cord type A fibers inhibit inhibitory inter neurons (gate keeper) and closes the gate at spinal cord level. So that pain is not perceived by brain (Ronald Melzack and Patrick D. Wall⁶).

TREATMENT METHODS OF OSTEOARTHRITIS

Pharmacological treatment:

Pharmacological treatment as commonly practiced medical interventions have their significance in the context of osteoarthritis patients. Though this approach is prevailing across last decade, adverse effects of treatments with pharmacological interventions (through application of pharmaceuticals) are reported and therefore have been vehemently criticized. Among most commonly recommended drugs for treating osteoarthritis patients, Acetaminophen (ER 1300mg 3 times daily) is found to be effective drugs by Prior MJ et al⁷ to relieve signs and symptoms of osteoarthritis patients with knee pain. Its reported adverse effects include angina pectoris, hypertension, dehydration, gastritis, urosepsis, atrial fibrillation, renal cyst, renal mass, congestive cardiac failure and dyspnea. Paracetamol as a pharmacological treatment is reported to have negligible effects in relieving signs and symptoms of osteoarthritis patients with knee pain. Cardiovascular problems, gastro intestinal bleeding, kidney problems, liver failure and toxicity has been reported with use of paracetamol (Machado GC et al⁸). While reporting about use of acetaminophen and NSAIDs, Richette P et al⁹ recommended low dose for short duration to minimize its side effects on cardiovascular and gastrointestinal tract. Contradictory to above findings Verkleij SPJ et al¹⁰ concluded that diclofenac and paracetamol do not exhibit significant difference in KOOS pain scale and diclofenac exposed group experienced greater adverse effects on gastrointestinal, respiratory, skin and

psychiatric problems than the group exposed to paracetamol alone.

Keller HL et al¹¹ reported that use of celecoxib and diclofenac slow release plus omeprazole in geriatric arthritis patients produced gastro intestinal adverse effects and death were reported in some cases who used celecoxib and diclofenac slow release plus omeprazole. Pareek A et al¹² concluded aceclofenac 100mg bid showed better gastro intestinal tolerability than diclofenac 50 mg tid, with reduced adverse events like abdominal pain, dyspepsia, dysphagia, nausea, constipation, diarrhoea and vomiting. Even Sugano K et al¹³ and Rogoveanu OC et al¹⁴ commented that prolong usage of NSAIDs in arthritis patients is associated with gastrointestinal events. On the other hand Bello AE et al¹⁵ found that usage of ibuprofen 800 mg plus famotidine 26.6mg resulted in better gastro intestinal protection than Ibuprofen alone in osteoarthritis patients. However, certain side effects like nausea, dyspepsia, upper abdominal pain, gastritis and hypertension were noticed. In addition to gastro intestinal adverse events Essex MN et al¹⁶ noticed central nervous system adverse events in Asian patients using NSAIDS like celecoxib and naproxen. In 2017 Gordo AC et al¹⁷ concluded celecoxib usage resulted in better tolerability in osteoarthritis knee patients with reduced gastrointestinal adverse events.

Opioids are also used commonly to treat symptoms of Osteoarthritis knee patients. Steigerwald I et al¹⁸ and Etropolski M et al¹⁹ suggested that tapentadol (50-250mg bid) usage in chronic Osteoarthritis knee patients showed better gastro intestinal tolerability but with diarrhoea, dyspepsia, headache, nausea, dizziness, constipation, hyperhidrosis, drug withdrawal syndrome, fatigue as adverse events. They also noticed adverse effects in nervous system.

Glucosamine and Chondroitin sulfate are nutritional supplements used to treat Osteoarthritis knee patients.

Hochberg MC et al²⁰ & Roman Blas J A et al²¹ noticed allergic dermatitis, dizziness and gastritis with its use.

Intraarticular injection is an alternate mode of treating Osteoarthritis knee. Corticosteroids, hyaluronic acid and plasma rich platelets (PRP) injections have been used in treating Osteoarthritis of knees. Steroid injections does not result in improved symptoms in all patients. Hyaluronic acid injection is an expensive viscosupplement and it is under debate whether it can be a treatment choice for Osteoarthritis knee patients. Glucocorticoid injection in Osteoarthritis patients resulted in post injection flare up to 10% patients and may cause septic arthritis in 0.08% (Yusuf E⁴). Huang PH et al²² conducted a study on PRP injection in treatment of Osteoarthritis knee. They found PRP treatment to be expensive and single or two injection per month found improvement in knee function only after 12 months of treatment, whereas 3 injections per month yielded significantly improved results in short term follow up.

Though the above discussed pharmacological treatments had some beneficial effects it is also associated with side effects. This is predominantly due to longer duration of treatment needed in these cases. Intraarticular injections, especially Hyaluronic acid and PRP can be expensive and may be not affordable by all patients. This is extremely important in India where majority of patients with Osteoarthritis knees are poor and struggle to bear the cost of treatment. Pharmacological treatments are not curative and improvement in symptoms is dose dependent. Considering all the above inhospitable events caused by pharmacological treatment there is need for a non pharmacological treatment which is safe and effective in treating knee osteoarthritis.

Non Pharmacological Treatment

Non pharmacological treatments are practiced as surrogate ways to treat Osteoarthritis knee patient. Among them

following are ubiquitously used methods. Thermotherapy which is one of the conventional method to treat Osteoarthritis knee patient, where heat, cold and combination of two (contrast bath) are used. Thermotherapy reduced symptoms of Osteoarthritis knee patients in short term in study of Amal E. shehata & Manal E. Fareed²³. Dantas L.O et al²⁴ reported that use the of cryotherapy improves functional activities of Osteoarthritis knee patients but its effect is only for short term.

Considering exercise as a treatment option for Osteoarthritis knee, it cannot be given as primary treatment methods when pain factor is reckoned, rather it can be given as auxiliary. More over supervening exercise protocols by patients periodically may not be viable. There were minimal or negligible clinical trail evidence to substantiate exercise can alter mechanical load and structural disease progression in Osteoarthritis knee patients (Bennell K et al²⁵) with their sequel decline over time (Bennell K L et al²⁶ and Beumer L et al²⁷)

In Electrotherapy low, medium and high frequency currents were used to ease pain for short terms. Accretion of Transcutaneous Electrical Nerve Stimulator (TENS), Interferential current (IFT) and Short wave diathermy with exercise program not showed superfluous effects in Osteoarthritis knee patients (Atamaz FC et al²⁸). TENS reduces pain in Osteoarthritis knee patients but the results can't be generalized because studies were done with small sample size (Palmer shea et al²⁹). On the other hand ULUS Y et al³⁰ and Cakir S et al³¹ commented that Ultrasound (US) produced short term effects in relieving pain and improving functional activities and it can't be used as treatment adjunct.

Waller B et al³² showed therapeutic aquatic exercise improves symptoms of Osteoarthritis. But muscle cramps, dizziness, fall and contact dermatitis were some of the adverse events reported with this treatment modality. Maintaining pool

temperature and its hygiene which is imperative for this treatment can be arduous.

Though massage is a form of non pharmacological treatment for Osteoarthritis patients and yields beneficial effects in patients with knee osteoarthritis. However, this form of treatment is time consuming posing logistical challenge (Atkins DV et al³³). Also massage when combined with exercises, produced negligible short term effects in Osteoarthritis knee patients (Godoy VC et al³⁴ and Bervoets DC et al³⁵).

Besides the treatments mentioned above, these days researchers are focusing on regenerative medicine to treat Osteoarthritis knee patients. Injection of mesenchymal stem cells into knee joint has shown to relieve pain ,improve cartilage quality, improve ROM and functional activity of knee joint (Koh YG et al³⁶, Orozco L et al³⁷, Vega A et al³⁸, Yokota N et al³⁹). Concept of mesenchymal stem cells is attractive but its results in human knee joint are primitive and majority of well documented results have been shown only in animal studies.

Finally when all the pharmacological and Non pharmacological treatments fails, surgical treatment may be necessary. This predominantly involves arthroplasty. Total Knee Arthroplasty is a very successful operation but it also has many potential complications. These include post operative deep infection, stiffness of knee joint, deep vein thrombosis ,pulmonary embolism, patellar subluxation, intraoperative fracture and joint instability(Skou ST et al⁴⁰) . In some cases there can be intraoperative and postoperative blood loss requiring blood transfusion (Jia li et al⁴¹). A high quality evidence with large sample size study is desirable comparing total knee replacement with non surgical interventions (Skou ST et al⁴²).

Patients are skeptical for surgical treatment as because of its associated complications as mentioned above. On the other hand patients who choose pharmacological and non

pharmacological treatments know that its effect is dose dependent and these treatments are not curative. Due to this there is scope for new innovative treatment for Osteoarthritis which can control symptoms without significant side effects. Using the body's own biological mechanism (ie) stimulation of mechanoreceptors in muscle and joint relieves pain, increase Active Range of Motion (AROM) and functional activities of Osteoarthritis knee patients. Mechanoreceptors which responds to mechanical stimulus are present in muscle and joints. Mechanical forces can be produced by PJM and PNF stretching techniques. By supporting the above statement, Nor Azlin MN and K. Sulyn⁴³ reported passive joint mobilization with conventional physiotherapy treatments provided good results in Osteoarthritis knee. Kadu SS et al⁴⁴ commented that PJM is safe, effective and well tolerated by Osteoarthritis knee patients and yielded colossal effects in controlling symptoms of Osteoarthritis when combined supervised clinical exercise. In Osteoarthritis knee patients, Maitland mobilization resulted in greater relief in pain and increase range of motion. Manual therapy are effective and safe for reducing pain, stiffness and increase functional activities of joints (Rangey PS et al⁴⁵ and Courtney CA et al⁴⁶).

PNF stretching, when applied to shortened hamstring muscle increased muscle flexibility and muscle activity which in turn end up in reduced pain and increased AROM of knee joint (LIM KL et al⁴⁷ and Kaur Mandeep⁴⁸). PNF technique when applied alone (Hold relax technique) produced increased muscle strength, range of motion and reduced pain in Osteoarthritis patients. Moreover modified hold relax resulted in increasing hamstring flexibility and reduced pain and disability overtime (Mistry GS et al⁴⁹ and Singh AK et al⁵⁰). Similarly when PNF combined with Dynamic stretching and myofascial release altogether increased passive knee extension with $\geq 20^\circ$ deficit (Deuyzman L et al⁵¹). In case of patello femoral pain syndrome,

PNF stretching produced positive effects (Golpayaegani M and Emamai SH⁵²).

All the available treatment methods for Osteoarthritis knee discussed above are good in relieving symptoms. However results yielded by mechanoreceptors unveils that PNF stretching and PJM techniques produced good results without side effects. Besides being safe they are also cost effective and may provide long term relief form symptoms with regular treatment sessions. These techniques are simple, can be easily taught to patients and can be done by patients on their own in domiciliary setting.

CONCLUSION

Pharmaceutical interventions currently dominate the treatment of Osteoarthritis knees. Non-pharmacological interventions in form of PNF stretching and PJM is safe and have potential to provide long term improvement in symptoms with negligible side effects. These treatment options are both underutilized and under reported. Authors feel that there is scope to explore these innovative treatment through mechanoreceptors to fill the existing gap in treatment of Osteoarthritis knee.

REFERENCES

1. Kelli D. Allen, Yvonne M. Golightly. Epidemiology of osteoarthritis: state of the evidence. *Curr Opin Rheumatol*, 2015 ; 27(3): 276–283.
2. Haq I, Murphy E, Dacre J. Osteoarthritis. *Postgrad Med J*, 2003; 79:377–383.
3. Chandra Prakash Pal, Pulkesh Singh, Sanjay Chaturvedi et al, Epidemiology of knee osteoarthritis in India and related factors. *Indian J Orthop*, 2016;50(5): 518–522.

4. Erlangga Yusuf MD, PhD, Pharmacologic and Non-Pharmacologic Treatment of Osteoarthritis. *Curr Treat Options in Rheum* 2016; 2:111–125
5. Kayla B. Hindle, Tyler J. Whitcomb, Wyatt O. Briggs et al. Proprioceptive Neuromuscular Facilitation (PNF): Its Mechanisms and Effects on Range of Motion and Muscular Function. *Journal of Human Kinetics* volume 31/2012; 105-113.
6. Ronald Melzack, Patrick D. Wall. Pain Mechanism: A New Theory. *Science* 1965;Vol.150: 971-979.
7. Mary Jane Prior, Diane D. Harrison, Mary Ellen Frustaci. A randomized, double-blind, placebo-controlled 12 week trial of acetaminophen extended release for the treatment of signs and symptoms of osteoarthritis. *Current Medical Research and Opinion* Vol. 30, No. 11, 2014;2377–2387.
8. Machado GC, Maher CG, Ferreira ML. Lack of efficacy of paracetamol (acetaminophen) for low back pain and osteoarthritis. *J Pioneer Med Sci* 2015; 5(4):142-143.
9. Pascal Richette, Augustin Latourte, Aline Frazier. Safety and efficacy of paracetamol and NSAIDs in osteoarthritis: which drug to recommend? *Expert Opin. Drug Saf.* (2015) 14(8).
10. SPJ Verkleij, PAJ Luijsterburg, SP Willemsen et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. *British Journal of General Practice*, August 2015.
11. Herbert L. Kellner, Chunming Li, Margaret N. Essex. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial. *Curr Med Res Opin* 2012; 28:1537–45.
12. Anil Pareek, Nitin Chandurkar. Comparison of gastrointestinal safety and tolerability of aceclofenac with diclofenac: a multicenter, randomized, double-blind study in patients with knee osteoarthritis. *Current Medical Research & Opinion* Vol. 29, No. 7, 2013, 849–859.
13. Kentaro Sugano, Yoshikazu Kinoshita, Hiroto Miwa et al. Safety and efficacy of long-term omeprazole 20 mg in Japanese

patients with a history of peptic ulcer receiving daily non-steroidal anti-inflammatory drugs. *BMC Gastroenterology* 2013, 13:54.

14. Rogoveanu OC, Streba CT, Vere CC, et al. Superior digestive tract side effects after prolonged treatment with NSAIDs in patients with osteoarthritis. *Journal of Medicine and Life* 2015; 8: 458-461 .

15. Alfonso E. Bello, Jeffrey D. Kent, Robert J. Holt. Gastroprotective efficacy and safety of single tablet ibuprofen/famotidine vs ibuprofen in older persons. *Phys Sportsmed*, 2015; 43(3): 193–199.

16. Margaret N. Essex, Michael A. O'Connell, Regina Behar, et al. Efficacy and safety of nonsteroidal anti-inflammatory drugs in Asian patients with knee osteoarthritis: summary of a randomized, placebo-controlled study, *International Journal of Rheumatic Diseases* 2016; 19: 262–270.

17. Ana C Gordo, Chris Walker, Beatriz Armada et al. Efficacy of celecoxib versus ibuprofen for the treatment of patients with osteoarthritis of the knee: A randomized double-blind, non-inferiority trial. *Journal of International Medical Research* 2017; 45(1); 59–74.

18. Ilona Steigerwald, Michael Schenk, Uwe Lahne et al. Effectiveness and Tolerability of Tapentadol Prolonged Release Compared With Prior Opioid Therapy for the Management of Severe, Chronic Osteoarthritis Pain. *Clin Drug Investig* (2013) 33:607–619.

19. Mila Etropolski, Brigitte Kuperwasser, Maren Flugel. et al. Safety and Tolerability of Tapentadol Extended Release in Moderate to Severe Chronic Osteoarthritis or Low Back Pain Management: Pooled Analysis of Randomized Controlled Trials. *Adv Ther* (2014) 31:604–620.

20. Marc C Hochberg, Johanne Martel-Pelletier, Jordi Monfort et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind,

non-inferiority trial versus celecoxib. *Ann Rheum Dis* 2016;75:37–44.

21. Jorge A. Roman-Blas, Santos Castaneda, Olga Sanchez Pernaute et al. Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis. *Arthritis and Rheumatology* Vol. 69, No. 1, January 2017, pp 77–85

22. Po-Hua Huang, Ching-Jen Wang, Wen-Yi Chou, et al. Short-term clinical results of intra-articular PRP injections for early osteoarthritis of the knee. *International Journal of Surgery* 42 (2017) 117-122

23. Amal E. Shehata and Manal E. Fareed. Effect of cold, warm or contrast therapy on controlling knee osteoarthritis associated problems. *International Scholarly and Scientific Research and Innovation* 7(9) 2013.

24. L.O. Dantas, C.C. Breda, P.R. Mendes Silva Serrao et al. Cryotherapy short-term use relieves pain, improves function and quality of life in individuals with knee osteoarthritis- A Randomized controlled trial. *Osteoarthritis and Cartilage* 25 (2017).

25. Kim Bennell, Rana S. Hinman, Tim V. Wrigley et al. Exercise and Osteoarthritis: Cause and Effects. *Compr Physio* 2011. 1:1943-2008,

26. Kim L. Bennell, Fiona Dobson, Rana S. Hinman. Exercise in osteoarthritis: Moving from prescription to adherence. *Best Practice & Research Clinical Rheumatology* 28 (2014); 93–117

27. Lucy Beumer, Jennie Wong, Stuart J Warden et al. Effects of exercise and manual therapy on pain associated with hip osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med* 2015;0:1–7

28. Funda C. Atamaz, MD, Berrin Durmaz, MD, Meltem Baydar, MD et al Comparison of the efficacy of transcutaneous electrical nerve stimulation, interferential currents, and shortwave diathermy in knee osteoarthritis: a double-blind,

randomized controlled multicenter study. *Arch Phys Med Rehabil* 2012;93:748-56.

29. Shea Palmer, Melissa Domaille, Fiona Cramp et al. Transcutaneous electrical nerve stimulation as an adjunct to education and exercise for knee osteoarthritis: a randomized controlled trial. *Arthritis Care & Research* Vol. 66, No. 3, March 2014, pp 387–394.

30. Yasemin Ulus, Berna Tander, Yesim Akyol et al. Therapeutic ultrasound versus sham ultrasound for the management of patients with knee osteoarthritis: a randomized double-blind controlled clinical study. *International Journal of Rheumatic Diseases* 2012; 15: 197–206

31. Cakir S, Hepguler S, Ozturk C et al. Efficacy of Therapeutic Ultrasound for the Management of Knee Osteoarthritis- A Randomized, Controlled, and Double-Blind Study. *Am. J. Phys. Med. Rehabil*, Vol. 93, No. 5, May 2014

32. Benjamin Waller, Anna Ogonowska-Slodownik, Manuel Vitor et al. Effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarthritis: systematic review with meta-analysis. *Phys Ther.* 2014; 94:1383–1395.

33. Dorothea V. Atkins PhD, David A. Eichler, PhD. The Effects of Self-Massage on Osteoarthritis of the Knee: a Randomized, Controlled Trial. *International Journal of Therapeutic Massage and Bodywork*- Volume 6, Number 1, March 2013.

34. Virginia Cortes Godoy, Tomas Gallego Izquierdo, Irene Lazaro Navas et al Effectiveness of massage therapy as co-adjuvant treatment to exercise in osteoarthritis of the knee: A randomized control trial. *Journal of Back and Musculoskeletal Rehabilitation* 27 (2014); 521–529

35. Diederik C Bervoets , Pim AJ Luijsterburg, Jeroen JN Alessie et al Massage therapy has short-term benefits for people with common musculoskeletal disorders compared to no treatment: A systematic review. *Journal of Physiotherapy* 61 (2015); 106–116.

36. Yong-Gon Koh, M.D., Seung-Bae Jo, M.D., Oh-Ryong Kwon, M.D et al. Mesenchymal Stem Cell Injections Improve Symptoms of Knee Osteoarthritis. *Arthroscopy: The Journal of Arthroscopic and Related Surgery*; 2013: pp 1-8.
37. Lluís Orozco, Anna Munar, Robert Soler, et al. Treatment of Knee Osteoarthritis with Autologous Mesenchymal Stem Cells: A Pilot Study. *Transplantation* & Volume 95, Number 12, June 27, 2013.
38. Aurelio Vega, MD, PhD, Miguel Angel Martin-Ferrero, MD, PhD, Francisco Del Canto, MD, et al. Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. *Transplantation* 2015;99: 1681–1690.
39. Naomasa Yokota, Masayuki Yamakawa, Tomohiko Shirata, et al Clinical results following intra-articular injection of adipose-derived stromal vascular fraction cells in patients with osteoarthritis of the knee. *Regenerative Therapy* 6 (2017); 108-112.
40. Soren T Skou, Ewa M Roos, Mogens B Laursen, Total knee replacement plus physical and medical therapy or treatment with physical and medical therapy alone: a randomised controlled trial in patients with knee osteoarthritis (the MEDIC-study) *BMC Musculoskeletal Disorders* 2012, 13:67
41. Jia Li, MD, Jinzhu Zhao, MD, Chongru He, MD, Comparison of Blood Loss After Total Hip Arthroplasty Between Ankylosing Spondylitis and Osteoarthritis. *The Journal of Arthroplasty* 31 (2016) ;1504-1509
42. Soren T. Skou, P.T., Ph.D., Ewa M. Roos, P.T., Ph.D., Mogens B. Laursen, M.D., Ph.D, A Randomized, Controlled Trial of Total Knee Replacement. *Engl J Med* 2015; 373:1597-606.
43. Nor Azlin m.n, k. Su Lyn. Effects of Passive Joint Mobilization on Patients with Knee Osteoarthritis. *Sains Malaysiana* 40(12)(2011): 1461–1465.

44. Dr. Mrs. Swati Sandeep Kadu, Dr Subhash Khatri, Dr Tejas Suryavanshi Effectiveness between supervised clinical exercise with Maitland manual therapy and Home exercise program in treating osteoarthritis of knee: Comparative study Indian Journal of Basic and Applied Medical Research; December 2013: Vol.-3, Issue-1, P.105-112.
45. Priya Singh Rangey, Megha S. Sheth, Neeta J. Vyas Comparison of Immediate Effect of Two Different Maitland Mobilization Protocols on Pain and Range of Motion in Subjects with Osteoarthritis of Knee International Journal of Medical and Health Research Volume: 1, Issue: 2, 26-29; Sep 2015
46. Carol A. Courtney PT, PhD, Alana D. Steffen PhD, Cesar Fernandez-de-las- Penas PT, PhD. Joint mobilization enhances mechanisms of conditioned pain modulation in individuals with osteoarthritis of the knee Journal of Orthopedic and sports physical therapy.2016
47. Kyoung Lim, PT, MSc, Hyung-Chun Nam, PT, PhD, Kyoung-Sim Jung, PT, PhD Effects on Hamstring Muscle Extensibility, Muscle Activity, and Balance of Different Stretching Techniques J. Phys. Ther. Sci. 26: 209–213, 2014
48. Mandeep Kaur, Rajesh Paul, Sandeep Kumar et al. A Randomized Controlled Trial to Compare the Effectiveness of Static Stretching Versus PNF Stretching of Hamstring Muscles Following Superficial Heat in Athletes International Journal of Scientific and Research Publications, Volume 4, Issue 7, July 2014.
49. Gopi S. Mistry, Neeta J. Vyas, Megha S. Sheth. Comparison Of The Effect Of Active Release Technique Versus Proprioceptive Neuromuscular Facilitation Stretching (Modified Hold-Relax) On Hamstring Flexibility In Patients Having Chronic Low Back Pain. NJIRM 2015; Vol. 6(5) Sept-Oct
50. Amit Kumar Singh, Sibbala Nagaraj, Rakesh Man Palikhe et al. Neurodynamic sliding versus PNF stretching on hamstring flexibility in collegiate students: A comparative

study International Journal of Physical Education, Sports and Health 2017; 4(1): 29-33

51. Laura Deguzman The Immediate Effects Of Self-Administered Proprioceptive Neuromuscular Facilitation, Myofascial Release, And Dynamic Stretching On Range Of Motion 2016.

52. Golpayegani M, Emami SH. The effect of proprioceptive neuromuscular facilities (PNF) stretching exercise on patellofemoral pain syndrome (PFPS)Scientific Journal of Kurdistan University of Medical Sciences No.87/Mar-Apr 2017.