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ORIGINAL STUDY

Conservative treatment of knee osteoarthritis

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Osteoarthritis of the knee causes chronic knee pain, loss of function and disability in the ageing population. When no treatment is applied, a guaranteed onset of symptoms and/or structural damage can be observed in the diseased knee. This work reviewed the different published guidelines, proposing combinations of weight reduction, physical therapy and rehabilitation, self-management education programs and pharmacological treatment. Randomized clinical trials, systematic reviews and guidelines were identified using the databases PubMed and Web of Science. Specific journals and reference lists were investigated. Sixty high quality articles were included concerning the conservative treatment of knee osteoarthritis. Weight loss when BMI > 28kg/m²; aerobic, proprioception and strengthening training; NSAIDs (ibuprofen, diclofenac, aceclofenac), IA corticosteroid and IA hyaluronic acid has the highest evidence. To achieve the greatest positive clinical and structural outcome, a combined conservative therapy is recom-mended.

Keywords : knee osteoarthritis; conservative; weight reduction; physical therapy; placebo; pharmacology; education; self-management.

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative joint disorder worldwide leading to disability in daily living *(25,29,31,52)*. It is highly prevalent among the ageing population and is diagnosed in approximately 10% of men and 18% of women older than 60 years *(5,29,57,58)*. OA occurs most frequently in the hip and the knee joint *(27,31,57)*. In the knee joint, the medial tibiofemoral compartment is the most frequently affected *(9)*. OA can be defined by clinical symptoms as well as by radiography *(29)*. The most common clinical symptoms of OA are pain, loss of function, joint stiffness and occasionally crepitus and effusion can be present *(5,25,31,38,57,60)*. Based on radiography, OA is characterized by progressive degeneration of the articular cartilage *(5,12,17,19,57)*. This cartilage degeneration includes osteophyte formation, subchondral cysts, joint space narrowing and sclerosis of the subchondral bone *(12,17,27,29)*. The presence of symptoms only, can lead to the clinical diagnosis of OA *(29)*. The disadvantage is that at that moment, OA is already advanced and probably irreversible *(29)*. Furthermore, the treatment of OA is more likely to be successful at early stages *(29)*. In general, radiography is used for the diagnosis *(19,29)*. For identifying early cartilage changes, magnetic resonance imaging is more

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sensitive *(29)*. Ultrasonography has the capacity to detect synovitis, which is another common element in OA *(29)*.

The main risk factors related to knee OA can be divided into two subgroups, the modifiable risk factors and the non-modifiable factors. One of the main modifiable risk factors is obesity *(21,57,60)*. A clear relation is shown between weight bearing and the development of OA, this correlation probably has a multifactorial origin *(13)*. The presence of high levels of insulin in the blood seen in obese subjects with OA would play a role in the development of OA compared to obese subjects without OA *(13)*. Furthermore, the co-existence of quadriceps weakness in subjects with obesity may lead to a greater loading on the articular cartilage of the knee during gait *(13)*. In general, quadriceps weakness is a risk factor in the development and progression of knee OA *(35)*. Pro-inflammatory cytokines are also present in obese patients, making the cartilage more susceptible for further degeneration *(13)*. Also a strong relation between body mass index (BMI) and OA is demonstrated *(47)*. Limited evidence indicated that malalignment of the knee is correlated with the occurrence of knee OA, whereas strong evidence is found for the correlation with progression of knee OA *(51)*. Specific physical activities during work is a risk factor, especially jobs involving frequently and long periods of kneeling or squatting *(21)*. Physical activity during leisure time could be a potential risk factor but still a lot of controversial results are found *(21)*. Thereby, there is a potential risk of injury while performing leisure and professional activities, which is a non-modifiable risk factor as mentioned below.

Non-modifiable risk factors are older age, female gender, previous injury or surgery of the knee and OA of other joints *(21,57,58)*.

RESULTS

The prevention and management of OA is a high priority worldwide *(57)*. As an intervention has more potential in early stages of OA, an early diagnosis is crucial *(29)*. Treatment needs to target both structural changes as well as improvements in clinical presentation *(29)*.

Weight reduction

Symptom relief following weight loss was proven over a short period, while there is no consensus over the long term *(13)*. A significant decrease in functional disability was seen in obese patients with a weight reduction of 5% achieved within a 20-week period, while it had less influence on the pain level *(18)*. Another study with an 18-month follow-up, included participants with a BMI $\geq$ 28kg/m^2 and compared a "high weight loss group" (> 5% reduction baseline body weight) to a "low weight loss group" (< 5%) and a "no weight loss group" *(40)*. Greater weight reduction resulted in lower maximum knee compressive forces, due to reduced hamstring co-contraction levels and significantly lower vertical ground reaction forces *(40)*. Furthermore, a significantly increase in walking velocity was found in the high and low weight loss group *(40)*. In an 18-month trial, patients with a BMI $\geq$ 28 kg/m^2 got subdivided in 4 groups, a healthy lifestyle (control) group, a diet only group, an exercise only group and a diet plus exercise group *(41)*. The diet-only group and the combined group had a significant weight reduction (±5%) relative to the healthy lifestyle group, with the combined group showing the best overall results in pain, physical function and measures of mobility and a long-term weight loss *(41)*. Rejeski WJ et al. used the same study protocol examining quality of life (QoL), with the combined group showing the greatest amelioration *(46)*. A weight reduction of ±5% was present in the diet and combined group *(46)*. Again, the same protocol was used, examining the effect on serum levels of cartilage oligomeric protein, hyaluronan (HA), antigenic keratin sulphate (AgKS) and transforming growth factor-β1 (TGF- β1) *(19)*. At baseline a negative correlation was found between levels of HA and medial joint space width and between TGF- β1 and Kellgren-Lawrence scores and a positive correlation between HA and Kellgren-Lawrence scores *(19)*. AgKS levels decreased slightly with each interventions, while the three other serum levels remained con-stant *(19)*. Another study examined extreme loss of weight (-20%), achieved by gastric surgery *(47)*. It seemed to improve pain, stiffness, function, low-grade

inflammation and cartilage turnover assessed by change in levels of joint biomarkers *(47)*. In general, no effect on Kellgren-Lawrence or joint structures scores was observed after any intervention *(19,40,41)*. However it could be concluded that they do not harm the joints in overweight and obese patients *(19)*.

In general it was found that a weight reduction of ±5%, in overweight patients with knee OA, seemed to ameliorate pain and function levels and the quality of life.

Physical activity and rehabilitation

Another main recommendation is physical activity and rehabilitation, with the intensity of exercises still being controversial. In a systematic review, high-intensity programs compared to control seemed to have greater and more lasting positive effects for knee strength *(58)*. While, low-intensity programs had only short term effect *(58)*. Another review found no important clinical benefit of high vs low intensity programs, based on low quality studies *(45)*. Joshua NF et al. compared a self-management program (SM) to a combined program of SM and progressive resistance training *(32)*. Both the combined group and the SM group increased their moderate- and vigorous-intensity physical activity levels significantly over short-term (3 months), only the combined group could maintain these changes at 9 months *(32)*. Lange AK et al. found that isolated progressive resistance training improved OA symptoms, physical function and muscle strength for 50-75% of the studies, being of clinical value, compared to usual care *(35)*. In addition, all physical performance measurements improved significantly in 50-100% of the studies for resistance training relative to a control, except for one (walk time) *(35)*. Conflicting results were present for the psychological domains of the 36-item Short Form Health Survey (SF-36) and health-related QoL *(35)*. In a RCT, patients with medial knee OA and varus malalignment got subdivided in a home exercise program and a control group *(11)*. The home exercise program consisted of strengthening exercises, including hip abductor and adductor strengthening *(11)*. A significantly clinical larger improvement was observed in the strengthening group for all measurements of pain, physical function, hip abductor and adductor strength and knee extension strength, whereas no difference was seen in external knee adduction moment *(11)*. Thus, hip strengthening did not influence medial knee load and it therefore seemed unlikely to influence joint structures *(11)*. Land-based therapeutic exercises significantly improved pain levels, QoL and physical function, up to 2-6 months *(10,25)*. Also muscle strength and walking ability showed improvements *(10)*. Therapy programs should be adjusted according to the patients biomechanical presentation (varus thrust, obesity) *(10)*.

Jansen MJ et al. found that adding passive manual mobilisation to an exercise intervention resulted in greater pain relief compared to exercise or strength therapy alone, while no significant difference was found in physical function *(31)*. A RCT evaluated the effect of manual therapy and/or exercise therapy in addition to usual care compared to usual care alone *(2)*. Both manual therapy and exercise therapy were significantly superior to usual care, no added benefit was observed in the combined group *(2)*. Another RCT found that adding 12 sessions of manual therapy to exercise therapy was superior to 12 consecutive exercise sessions alone *(1)*. Furthermore, 12 booster exercise sessions resulted in a greater effect compared to 12 consecutive sessions *(1)*. Adding both, booster sessions of exercise therapy and manual therapy had no beneficial effect compared to exercise therapy alone *(1)*.

Tai Chi induced improvements of pain, physical function and stiffness, which makes it a safe option as additional therapy *(26,36)*. This in contrast to a systematic review, that showed no significant positive effect of Tai Chi *(55)*. Hydrotherapy during a 12-week period seemed to improve physical function and pain, remaining up to 24 weeks *(26)*. The hydrotherapy group showed greater pain relief and significant ameliorations in physical performance measurements compared to a group performing Tai Chi *(26)*. A review showed that aquatic exercises (12 weeks) had small short-term but clinically relevant positive effects on joint pain, disability and QoL for a mixed group of knee and hip OA patients, causing no adverse events *(5,48)*.

In general, aerobic, aquatic, strengthening and proprioception exercises had positive effects on

pain, function and/or disability level *(55)*. Not a single intervention improved all outcomes *(55)*. Moderate quality evidence showed that high compliance in aerobic and strengthening exercises led to better outcomes *(55)*. Adverse events after therapy were rare *(55)*.

Rehabilitation interventions published since the Osteoarthritis Research Society International (OARSI) conference in April 2012 demonstrated that physical modalities, such as laser, interferential current, short wave diathermy, therapeutic ultrasound, radiation and transcutaneous electrical nerve stimulation (TENS), was not superior to sham control *(22)*. Same conclusion could be made for pulsed electrical stimulation *(24)*. A review of the Cochrane library did also find no benefits for TENS, while therapeutic ultrasound and electromagnetic field therapy may provide improvements *(48)*. In a systematic review pulsed electromagnetic fields, diathermy and magnetic stimulation reported no improvements on pain and/or function level, while ultrasonography seemed to have positive effect *(55)*.

Wageck B et al. compared the effect of Kinesio Taping and sham taping on pain and function, which showed no significant difference at the end of a 4-day application and 15 days later *(54)*. A systematic review did also find no positive effect of taping on pain and/or function level *(55)*. Further, acupuncture seemed to be of no clinical relevance *(10,48)*.

To summarize, one can conclude that physical activity and rehabilitation are likely to cause positive effect on many outcomes, such as pain level, physical function and performance and QoL. Especially land-based therapeutic exercises as well as hydrotherapy with the focus on resistance, aerobic, proprioception and strengthening training seem to provide benefit. Adding manual therapy can give a greater result. Regarding physical modalities, lot of controversial results are found.

Self-management education programs

These are behavioural sessions with the aim to motivate people with chronic diseases to take an active role in their disease management *(34)*. No or little benefits were found favouring behavioural sessions, however some people may gain large clinical benefit *(34,55)*. Williamson W et al. found that arthritis self-management programs had little, but significant short-term benefits in physical activity compared to control *(56)*. The greatest effect was seen in the first 12 months and declined with prolonged follow-up *(56)*. It seemed to be possible to control pain and symptoms and to prevent secondary complications *(56)*. An osteoarthritis self-management program (6 weeks) resulted in significant improvements in pain, function and QoL at 8 weeks and 6 months, compared to a control group, based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC *(7)*) and the SF-36 measurements *(20)*. Consequently, there seems to be an added clinical value when using education programs.

Braces and insoles

A 12-month RCT failed to show beneficial effects of lateral wedge insoles on symptoms or disease progression in subjects with medial knee OA, compared to neutral insoles *(9)*. Same comparison was done in a randomized crossover trial and a 24-month prospective RCT, with same results *(3,42)*. However, a greater adherence and a smaller non-steroidal anti-inflammatory drug (NSAID) intake was seen in the lateral wedge insole group *(42)*. Other studies showed no significant benefit for insoles in general *(10,16,23,48)*. But van Raaij TM et al. found that laterally wedged insoles may be an alternative treatment for valgus bracing (control) *(53)*. No differences in pain reduction or function and correction of varus malalignment were notable, but subjects treated with insoles showed greater compliance *(53)*. In subjects with unicompartmental knee OA, conservative treatment plus bracing showed small beneficial effects compared to conservative treatment alone in a 12-month follow-up *(15)*. These results showed only borderline significance *(15)*. The compliance for brace treatment was small due to small improvements or large adverse events *(15)*. Two Cochrane reviews found no or inconclusive results concerning bracing *(23,48)*. In general, biomechanical devices did not seem to be of clinical value *(55)*.

Pharmacological treatment

Non-steroidal anti-inflammatory drugs (NSAIDs)

A RCT of a 4-week intervention compared a NSAID, ibuprofen, in a high dose as anti-inflammatory (2400mg/day) and in a low dose as analgesic (1200mg/day), to acetaminophen (analgesic) *(14)*. Rest pain seemed to have a greater decrease in both ibuprofen groups compared to acetaminophen, while pain while walking, function and disability didn't differ significantly *(14)*. Adverse events seemed to be equal in all three groups, with the gastrointestinal tract most affected in the high dose of ibuprofen *(14)*. In a Cochrane review same result was found, NSAIDs resulted in greater pain relief compared to acetaminophen *(48)*. A 2-week treatment with oral celecoxib (200mg/day or 400mg/day) or ibuprofen (1200mg/day or 1800mg/day) or diclofenac (75mg/day or 150mg/day) seemed to suppress pro-inflammatory cytokines, relief pain and ameliorate function without serious adverse reactions *(28)*. Thereby higher dosage would cause greater improvements in QoL and a higher modulation of cytokine secretion *(28)*. A 6-week RCT compared aceclofenac (200mg/day) and paracetamol (3000mg/day), which resulted in a greater improvement of pain, function and overall assessment favouring aceclofenac and no difference in tolerability *(6)*. Moreover, withdrawal was higher in the group receiving paracetamol due to absence of efficacy *(6)*. Two years of treatment with glucosamine, chondroitin sulphate, the combination of those two or celecoxib showed no clinical relevant difference in WOMAC pain or function, compared with placebo *(49)*. A clinically symptomatic amelioration was present in all treatment groups, including placebo, yet glucosamine and celecoxib showed the greatest beneficial effects *(49)*. Adverse events in all four treatment groups were similar *(49)*. In a Cochrane review only small effects of glucosamine were reported *(48)*. Based on a meta-analysis of RCTs, diacerein was recommended as an alternative treatment for subjects with a contra-indication for paracetamol or NSAIDs *(4)*. A significant pain reduction was present in the first 6 months, yet no longer present after 6 months *(4)*. The diacerein group had an increased risk of diarrhoea compared to the placebo group *(4)*. Rodriquez-Merchan EC found only minor effects of diacerein *(48)*.

NSAIDs, such as ibuprofen, diclofenac, aceclofenac and celecoxib seem to provide improvements on many outcomes, this superior to acetaminophen.

Bisphosphonates

In a 2-year longitudinal study, subjects got divided into four groups, receiving placebo, risedronate 5mg/day, 15 mg/day or 50 mg/week *(17)*. Each group got subdivided into joint-space narrowing (JSN) non-progressor or JSN progressor (JSN $\geq$ 0.6mm of the medial compartment) *(17)*. In the JSN non-progressor groups no drug effect was seen on the trabecular bone *(17)*. While in the JSN-progressor groups subjects who received risedronate 15mg/day, the trabecular number of vertical trabeculae remained constant and in those receiving 50mg/week the number significantly increased *(17)*. The difference between JSN non-progressor and JSN progressor groups could be due to differences in level of bone turnover *(17)*.

Intra-articular (IA) injections

IA corticosteroids

A Cochrane review investigated the effect of IA corticosteroid *(33)*. Compared to control treatments, corticosteroid injections showed moderate and small improvements respectively in pain and physical function *(33)*. While no evidence of benefits was found in QoL or joint structures *(33)*. If IA corticosteroid provided clinically meaningful improvements after 1-6 weeks, remained unclear *(33)*.

IA corticosteroids vs. IA hyaluronic acid

IA corticosteroids showed short-term benefit superior to placebo with only few side effects, while hyaluronic acid seemed to have a later onset but a more durable benefit *(8)*. Leopold SS et al. investigated the efficacy of IA injection of betamethasone corticosteroid and Hylan G-F 20 *(37)*. Both treatments induced significant improvements in the WOMAC scores and non-significant improvements in Knee Society system scores, while only the Hylan G-F 20 group showed significant

improvements in the visual analogue scale for pain *(37)*. All the significant improvements were only of modest clinical value *(37)*. Nevertheless, despite these results, no significant difference was notable between the two intervention groups at 3 or 6 months *(37)*. Furthermore, women showed significantly less response than men for both treatments, on all outcome measurements *(37)*. Due to additional pain, risk at secondary complications and costs, injections of Hylan G-F 20 were not recommended as a first-line treatment *(37)*. Trojian TH et al. compared the effect between IA injections of hyaluronic acid, corticosteroids and placebo *(52)*. IA hyaluronic acid had small but significant improvements compared to the other two *(52)*. Subjects were 15% more likely to respond by the Outcome Measures in Rheumatoid Arthritis Clinical Trials - OARSI (OMERACT-OARSI *(43)*) criteria than subjects who got injected with corticosteroid and 11% compared to placebo *(52)*. High-quality evidence recommended IA hyaluronic acid for subjects with Kellgren-Lawrence grades II-III older than 60 and moderate quality evidence suggested IA hyaluronic acid for subjects under 60 *(52)*.

There seems to be no concensus about this topic. Both IA corticosteroids and hyaluronic acid seem to provide positive effects.

Dextrose injections

A 3-arm, blinded, randomized controlled trial was performed examining the effect of prolotherapy (dextrose injection) compared to saline injections (blinded) and home exercises (nonblinded) *(44)*. Subjects injected with dextrose showed significant and sustained improvements in pain, function and stiffness, assessed by the WOMAC and a significant reduction of the knee pain scale-based knee pain frequency and severity compared to the other two groups *(44)*. No adverse effects were reported *(44)*.

Other

Some authors have investigated the influence of some other drugs. It was found that the positive effects of tramadol, oral or transdermal opioids and doxycycline were small *(48)*. While the American Academy of Orthopaedic Surgeons clinical guidelines of evidence-based treatment recommendations for knee OA strongly recommended Tramadol *(16)*.

Placebo

A meta-analysis of RCTs indicated that placebo is an effective treatment in the management of OA, which could be concluded from improvements of subjective measurements such as pain, function, stiffness and doctor's global assessment *(59)*. No improvements in objective outcomes were notable *(59)*. As example, physical modalities had no benefit over placebo control, but both showed significant improvements after treatment *(22)*. The magnitude of the effect of placebo is influenced by baseline severity of the disease, the expected strength of the treatment, the method of application and sample size *(59)*. Blinded placebo had a greater effect compared to open placebo, drug therapies was superior to non-drug therapies, whereby invasive application of drugs had greater effects than non-invasive and opioid placebo was more effective than herbal placebo *(59)*. All these data suggest that the higher the expected value of a treatment the higher the placebo effect *(59)*. Furthermore, a positive relation was seen between baseline pain and the effect of placebo and between sample size and the effect of placebo *(59)*. As previously mentioned, IA corticosteroids and IA hyaluronic acid seemed to be superior to placebo *(8,52)*.

Multiple treatments and combined therapy

Skou ST et al. compared a 12-week individualized, non-surgical therapy program of neuromuscular treatment, education, usage of insoles and, if recommended, a diet program and pain medication to usual care *(50)*. Clinically relevant long-term benefits for pain, function and QoL were identified after the combined non-surgical program, even for subjects with severe knee OA *(50)*. And no serious adverse effects were seen *(50)*.

The long-term effectiveness and costs of a treatment program including education, exercises and a self-management program was examined in patients with chronic knee pain and compared to usual care *(30)*. Great improvements were found

in subjects receiving the treatment program, these improvements diminished over time but were still present after 30 months *(30)*. There was a high probability that this treatment program was more cost-effective compared to usual care *(30)*.

Current guidelines

Ottawa Panel evidence-based guidelines recommended aerobic walking programs of 2 to 9 months combined with other therapies, such as education and multicomponent exercises, based on high quality evidence *(38)*. Great improvements in pain relief, functional status and QoL were present, reaching statistical significance and clinical importance *(38)*.

The American Academy of Orthopaedic Surgeons clinical guidelines of evidence-based treatment recommendations for knee OA strongly recommended self-management programs, strength and low-impact aerobic training, neuromuscular education, an active daily life and the use of topical or oral NSAIDs and Tramadol *(16)*. Combined proprioception, balance and strength training would be superior to strength therapy alone *(16)*. Weight loss is recommended for subjects with symptomatic OA and BMI $\geq$ 25 *(16)*. Especially the combination of diet and exercise therapy gave improved results *(16)*. High strength studies could not recommend acupuncture, glucosamine, chondroitin and IA hyaluronic acid, based on lack of efficacy *(16)*. Finally, no consensus could be made about the effect of manual therapy, valgus bracing, opioids or pain patches, growth factor injections and/or platelet rich plasma, due to lack of (relevant) articles *(16)*. And no recommendation could be made for acetaminophen, IA corticosteroids and the use of physical agents, due to inconsistent results *(16)*. However, there was evidence regarding effectiveness of ultrasound *(16)*.

The OARSI guidelines (2014) recommended land- and water-based exercises (aerobic and strength training + range of motion), self-management programs, education, weight management, acetaminophen, capsaicin and IA corticosteroid *(39)*. For subjects without comorbidity, oral non-selective NSAIDS, oral cyclooxygenase-2 inhibitors and topical NSAIDS were also recommended *(39)*. Strength training consisted of resistance-based and quadriceps exercises, weight bearing (WB) and non-WB exercises and both group and individual therapy *(39)*. Based on fair evidence, biomechanical interventions (braces, sleeves and orthoses), cane use and duloxetine seemed to be appropriate as well *(39)*. Furthermore, based on good quality evidence, inconclusive results were found for acupuncture, TENS, ultrasound, avocado soybean unsaponfiables, chondroitin, glucosamine, diacerein, IA hyaluronic acid, transdermal and oral opioids and rosehip *(39)*. Further, inconclusive results were present for balneotherapy, based on fair evidence, and for crutches due to lack of evidence *(39)*. Electrotherapy and risedronate were not recommended based on low quality *(39)*.

CONCLUSIONS

In general, no single intervention had positive effect on all outcomes, showing the importance of a combined conservative treatment in patients with knee OA. The conservative treatment of knee osteoarthritis should focus on a combination of weight management, physical therapy and rehabilitation, self-management education programs and pharmacological treatment. Physical exercise therapy programs should consist of a variety of exercises and treatments, such as analytic and functional exercises, proprioception, neuromuscular and strength exercises, aerobic training and many more. It is important to include weight bearing exercises as well as non-weight bearing exercises, group and individual sessions, supervised and home-based exercises and land-based and water-based interventions. Self-management programs need to focus on behavioural change, promoting exercise and disease coping strategies and an active daily life. Also, placebo treatments seem to have positive effects on symptoms. Finally, there are still lot of controversial results concerning pharmacological treatments. At this moment, the focus goes to acetaminophen, NSAIDs, opioids and IA injections of corticosteroid and hyaluronic acid.

After evaluation of the plenitude of papers describing the conservative treatment of knee osteoarthritis, we found that the following factors had the highest evidence: weight loss when BMI > 28kg/m^2; aerobic, proprioception and strengthening

training; NSAIDs (ibuprofen, diclofenac, aceclofenac), IA corticosteroid and IA hyaluronic acid. Future research should focus on these factors and explore the most clinically relevant treatment protocol.

List of abbreviations

AgKS	Antigenic keratin sulphate
BMI	Body mass index
HA	Hyaluron
IA	Intra-articular
JSN	Joint-space narrowing
mg	milligrams
NSAID	Non-steroidal anti-inflammatorydrug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT-OARSI	Outcome Measures in Rheumatoid Arthritis Clinical Trials - Osteoarthritis Research Society International
QoL	Quality of life
RCT	Randomised controlled trial
SF-36	36-item Short Form Health Survey
SM	Self-management
TENS	Transcutaneous electrical nerve stimulation
TGF- β1	Transforming growth factor-β1
WB	Weight bearing
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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