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Prospective, Multi-Center, Pilot Study to Evaluate Symptom Relief in Patients with Medial Knee Osteoarthritis (OA) Treated with the KineSpring® Knee Implant for Load Reduction – The SOAR Protocol

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ABSTRACT: The study described here is designed as a prospective, multicenter, open-label, single-arm pilot study. Eligible subjects with symptomatic osteoarthritis of the medial compartment of the knee will be enrolled in the study and will receive the KineSpring® Knee Implant System. The study population will consist of adult patients between 25 and 80 years of age that have been diagnosed with medial knee osteoarthritis and have failed to improve after at least 6 months of conservative medical treatment. A patient is considered to have a clinically important change in OA pain and function with a minimum improvement of 20% compared to baseline measures. We will collect data on the safety and effectiveness of the KineSpring in patients with primarily unicompartmental medial knee osteoarthritis through 24 months of postoperative follow-up. These data will provide insights on the overall clinical success and safety outcome of KineSpring System.

KEY WORDS: osteoarthritis, knee, study protocol

I. INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder and one of the most frequent causes of pain and disability.[1] In OA, articular cartilage and subchondral bone are gradually destroyed. As the bone surfaces become less well protected by cartilage, the patient experiences pain when weight bearing, including walking and

standing. The main symptom of osteoarthritis is chronic pain, which causes loss of mobility and often stiffness. As OA progresses, the affected joints appear larger, are stiff and painful, and usually feel worse the more they are used and loaded throughout the day. With progression in OA, the cartilage loses its viscoelastic properties and its ability to absorb load; thus, repeated excess loading advances the rate of damage to the knee, and a vicious cycle ensues. In an effort to reduce the pain from these activities, patients with OA are forced to exercise less, and this can dramatically impact their ability to perform daily activities and thus negatively affect their quality of life.

Osteoarthritis affects an estimated 15% of the world's population.[2] Knee OA is the most predominant form, and approximately 90% of symptomatic patients present primarily with medial-compartment knee OA.[2–5] The prevalence of OA will continue to rise with the increasing age and increasing lifespan of the population. This condition decreases functional independence and in some instances may impair the afflicted individual's ability to complete normal activities of daily living or to participate in age-appropriate recreational activities. Patients face progressive pain and disability for the remainder of their lives. In spite of the prevalence and the extensive study of the disease, no cure for OA has yet been identified.

There remains an absence of non-surgical modalities that clearly alter the natural history or prevent structural damage in OA of the knee. In short, OA is a process that is attempting to contain a mechanical problem in the joint. Thus, OA is defined as failed repair of damage that has been caused by excessive mechanical stresses or loading on joint tissues. Because the body's innate mechanisms for repairing the damaged tissues cannot be effective in the face of the underlying mechanical abnormality, they cannot solve the problem of OA; for example, remodeling of subchondral bone may reduce the excessive stress and contain the mechanical abnormality, but it may result in joint pain. OA has no common pathophysiologic pathway, only a final common end stage.[6] The inflammatory changes in OA are secondary and are caused by particulate and soluble breakdown products of cartilage and bone.

The aims of management of knee OA are (1) patient education about the disease and its management, (2) pain control, (3) improved function and decreased disability, and (4) altering the disease process and its consequences.

The management of OA should be individualized and consist of a combination of treatment options. In the absence of a cure, current conservative therapy primarily attempts to reduce pain and improve joint function by employing modalities targeted toward symptom relief that do not facilitate any improvement in joint structure. The recommended hierarchy of management consists of nonpharmacologic modalities initially, followed by drugs and then surgery. Several comprehensive guidelines have been developed that describe the management of knee OA, based on evidence from trials and expert consensus. Updated evidence-based, international consensus recommendations for the management of knee OA have been developed by the OARSI Treatment Guidelines Committee.[7] These recommendations include the level of research evidence supporting them, the effect size for pain relief (95% CI), the extent of consensus (%), and the strength of recommendation (mean ± SE) for each proposition.

A. Conservative Treatments

A number of conservative measures are recommended to alleviate symptoms of mild to moderate knee OA; however, there is little evidence to support the long-term efficacy of these interventions. The following subsections summarize the key findings for leading conservative care (nonpharmacologic and pharmacologic) modalities.

1. Education

Patients should be encouraged to participate in self-management programs (e.g., those conducted by the Arthritis Foundation), informed regarding the natural history of their disease (e.g., visiting the Arthritis Foundation website), and provided resources for social support and instruction on coping skills.[8]

2. Weight Loss

The most direct approach to joint unloading involves body weight loss. Indeed, body weight loss in obese patients lowers knee compressive forces, improves knee function, and alleviates OA knee pain.[9] The Arthritis, Diet, and Activity promotion trial showed that diet and exercise leads to overall improvement in self-reported measures of pain and function in older overweight and obese adults with knee OA,[10] even with loss of just 5% of their total weight over 18 months. An average 1 kg of weight loss results in a 4-kg reduction in knee compressive forces.[11] Even a modest 10-lb loss of body weight can lower the cumulative compressive forces at the knee by almost 50,000 lb for each mile walked. Felson et al. reported that body weight loss of 11 lb lowers the risk of developing OA by greater than 50%. Losing excess body weight and maintaining a lower body weight, however, can be extremely challenging. Only one of five people who embark on a weight loss program ultimately lose 10% or more of their initial body weight and maintain that loss for at least 1 year.[12]

3. Exercise

Exercise increases aerobic capacity, muscle strength, and endurance and also facilitates weight loss.[13] All persons capable of exercise should be encouraged to partake in a low impact aerobic exercise program. Quadriceps strengthening exercises have been demonstrated to lead to improvements in pain and function.[14–16]

4. Physical Therapy

Physical therapy consists of several strategies to facilitate symptom resolution and improve functional deficits, including range of motion exercise, muscle strengthening, muscle stretching, and soft tissue mobilization. Although the results of a recent randomized, double-blind, placebo-controlled trial found that regular contact with a therapist (sham ultrasound therapy) provided an equivalent effect in reducing pain and disability, the effects in both groups in symptom improvement were substantial.[17] Another randomized controlled trial focused more on quadriceps strengthening did show a benefit of physical therapy in OA of the knee.[18]

5. Knee Braces and Orthotics

Because involvement of the medial tibiofemoral compartment is especially frequent, interventions whose goal is to realign the knee to reduce transarticular loading on the medial compartment, such as valgus bracing, are sometimes used clinically. For persons with instability of the knee, evidence suggests that valgus bracing and orthotics shift the load away from the medial compartment and, in doing so, may provide considerable relief of pain and improvement in function. Randomized controlled trials revealed that there was an approximate 50% improvement in pain and function with valgus bracing, which is substantially more than is realized with NSAID administration.[19] However, it is well established that patient compliance is low over the long term.

6. Pharmacologic Approaches

Structure-modifying efficacy has not been convincingly demonstrated for any of the existing pharmacologic agents. Current drug-treatment paradigms reduce the symptoms of OA, but side-effect profiles are raising a number of legitimate concerns about their long-term safety,

especially COX-inhibitors.[20] Judicious use of topical NSAIDs has been demonstrated to be effective in relieving pain in knee OA when compared with placebo.[21] This route possibly reduces gastrointestinal adverse reactions by maximizing local delivery and minimizing systemic toxicity. Hyaluronic acid (HA) injections may provide relatively small and short-term relief of pain and improved functionality for patients with osteoarthritis of the knee, but benefits do not last beyond 6 months.[22]

In summary, although a wide range of conservative care options are available to patients with knee OA, each option suffers from distinct limitations. Initial management of knee OA symptoms utilizes conservative care including activity modification, weight loss, physical therapy, orthotics, and/or bracing, and pharmacologic approaches. However, their long-term efficacy is poor, and they may actually encourage greater mechanical loading of the medial compartment, resulting in accelerated OA progression. Patients who fail conservative care are likely to endure chronic pain, lower quality of life, and physical activity limitations, despite continued analgesic and anti-inflammatory medication use. Over time, the risk of weight gain, depression, chronic disease, and other conditions manifested by lack of physical activity may increase.

As the disease slowly progresses to cause moderate-to-severe pain and/or disability, invasive surgical treatment options such as total knee arthroplasty, unicompartmental arthroplasty, or high tibial osteotomy (HTO) may be considered in select patients with single-compartment disease.

C. Current Surgical Treatment Options

Once conservative care options have been exhausted, the patient is faced with a difficult decision: endure continued pain and disability while avoiding joint modifying surgery or undergo surgery and accept the associated risks and lifestyle modifications. Only 9–33% of patients with severe knee OA are willing to consider knee arthroplasty, largely because of the invasive irreversible nature of the procedure as well as the extended recovery time and potential need for future revision.[23–25]

The goal of surgical treatment for unicompartmental OA is to reduce pain, restore function, and improve quality of life.[26] Current surgical treatment options include knee arthroscopy, osteotomy, HTO, unicompartmental knee arthroplasty (UKA), partial knee replacement, and total knee replacement (TKR). Key issues in the selection of an appropriate surgical treatment for unicompartmental OA are intensity and duration of symptoms, patient age and activity level, general health, and associated factors such as ligament instability, malalignment and bony deformity.

Numerous studies have shown a correlation between load, disease progression, and pain in osteoarthritic knees, while joint load reduction plays an equally important role in the alleviation of OA.[27–31] Treatments aimed at reducing knee joint loads represent a compelling approach to decreasing pain and disability associated with medial knee OA. The most well-established surgical option performed to decrease knee joint load is a HTO procedure.

1. High Tibial Osteotomy

HTO is a procedure used to treat unicompartmental osteoarthritis of the knee. The goal of HTO is to change the load distribution across the knee to reduce pain, slow the degenerative process of osteoarthritis, and avoid or postpone total knee arthroplasty.[32,33] Young, active patients who are too young for a total knee replacement are good candidates for the procedure.[34] There are two techniques used to perform a high tibial osteotomy: a closed wedge osteotomy (CWO) or an open wedge osteotomy (OWO). An opening wedge cuts the bone, increases the angle, and fills the gap with a bone

graft.[35] A closed-wedge osteotomy removes a wedge of bone to achieve the change of angle.[36] A recent review of the CWO technique reported that, though this procedure is common, effective and well-established in the treatment of knee OA, it can result in significant complications.[37] Complications included fracture, neurovascular injury, delayed union and nonunion, thromboembolic disease, infection, and undercorrection or recurrence of deformity.

The value of osteotomy to correct malalignment has followed the principle of transferring load toward the unaffected knee compartment to relieve symptoms and slow disease progression. In patients with medial or lateral compartment osteoarthritis, an HTO can decrease joint loads, slow the progression of cartilage breakdown, or even aid in the repair of cartilage in the affected compartment.[38,39] The reported results of HTO vary considerably across the literature, but the procedure generally provides good relief of pain and restoration of function in approximately 80% to 90% of patients at 5 years and in 50% to 65% at 10 years.[40] Although HTOs have generally been shown to be clinically effective in reducing pain and disability, the surgical procedure is invasive, requires a significant amount of bone resection, and requires a relatively long postoperative recovery. However, reduction of the abnormally high stresses in an OA joint by osteotomy has been shown to result in gradual loss of the subchondral sclerosis radiographically and an increase in the formerly narrowed joint space.[41]

Certainly HTO is a technically demanding surgery, requiring a relatively long recovery and rehabilitation period. Additionally, the procedure can result in significant complications and increased surgical difficulty in converting to an arthroplasty, if needed.

2. Joint Unloading with External Joint Distraction

Joint distraction surgery provides complete unloading of the joint by means of an external distraction frame. External fixation rods are drilled through the skin into the bones of the thigh and shin, and the joint is distracted by way of an external fixation frame fitted with springs. Recent preliminary reports of the results of external joint distraction in treatment of severe symptomatic OA provide further evidence of the efficacy of joint unloading. Among 19 patients who had severe tibiofemoral OA who were candidates for joint arthroplasty, distraction of the knee joint for 2 months by way of an external fixation frame resulted in a striking reduction in joint pain and improvement in function and clinical status, with almost complete normalization by 6 months.[42] In 5 patients who have been followed for 2 years after undergoing knee distraction, the improvement has been sustained. Longitudinal MRI examinations suggest articular cartilage repair, with a 30% increase in total cartilage volume and a 25% increase in mean cartilage thickness, relative to baseline.

In subjects who had relatively mild structural changes of knee OA, Thorp et al.[31] found that those who had knee pain had significantly higher medial compartment loads than those who were asymptomatic, whereas loads in those who were asymptomatic were not different from those in normal controls. These results suggest that at this stage of structural damage, individuals who have symptomatic OA differ biomechanically from those who have asymptomatic disease.

It has become increasingly clear that pathologic overloading is intimately associated with progression of OA to end-stage disease. The close association of dynamic joint overloading with OA progression suggests that therapeutic strategies aimed at altering and reducing the loads borne by the medial knee, in particular, may have significant impact on the progression, and possibly the pain, associated with OA.

3. Knee Arthroplasty

The standard surgical treatment for end-stage OA knee is total knee arthroplasty (TKA). TKA

and its reportedly less-invasive counterpart, unicompartmental knee arthroplasty (UKA), modify the joint by replacing the damaged and painful articular regions, rather than modifying the loads. Pain relief is immediate and consistent; however, despite significant improvements, limited range of motion and material wear of TKA limit its use in younger, more active patients, and the systems are considered most applicable to more sedentary OA patients later in life, resulting in irreversible disruption of the joint. In UKA patients younger than 55, the risk of revision has been shown to be almost three times greater than that for patients older than 55 (24%).[43] Complications can be devastating to the patient and include bone fracture, stress fractures, neurovascular nerve injury, wound healing problems, and infection, all of which can lead to serious problems and the need for revision knee replacement.

In summary, surgical treatment options that modify joint loads adequately demonstrate the potential of load reduction to positively impact the OA knee. All have proven efficacious, have the benefit of preserving the native joint structure, and in some cases have the significant advantage of being less invasive than arthroplasty. However, none offer the reliability of outcome that arthroplasty provides, and ultimately this is their greatest limitation.

The evidence implicating joint loading, and more specifically joint overloading, in the OA process is well documented in the literature. Joint overloading correlates with incidence, symptom severity, radiographic, morphologic, and biological processes. Load-modifying treatments, including weight loss, valgus braces, HTO, external distraction devices, which clearly demonstrate symptom relief, pain reduction, and improved function, have been reported. Despite these positive results, both physicians and patients are frustrated with the inconsistent outcomes from these treatment options.

Given the increasing prevalence of OA in younger patients and the evident potential of load management to positively impact these patients, the pursuit of novel and innovative load-modifying therapies that overcome the limitations of the current treatment options is both warranted and necessary.

D. Rationale for This Study

The KineSpring® Knee Implant System is designed to treat pain and loss of function secondary to medial knee OA by absorbing joint overload. A complete system (one femoral base, one tibial base, and one absorber) is implanted subcutaneously on the medial side of the knee using standard orthopedic techniques. The bases are fixed to the bone using a series of bone screws, and each base is attached to a ball-and-socket joint that articulates with the central spring-like absorber component.

The KineSpring System is expected to reduce the load on the diseased surface within the knee by acting as an extra-articular supplemental load path to the affected joint. Additionally, the KineSpring System has no known detrimental effect on natural knee kinematics because it is implanted using relatively small incisions without disrupting bone, cartilage, ligaments, or other tissues or structures. Important advantages of the KineSpring System, especially for patients who want to remain active and healthy, include the potential for quick postoperative recovery and joint mobility, and the ability to preserve natural joint anatomy so that future surgical options remain open for the patient.

Currently, no device therapy exists that targets reduction of excess loading as its key method of action, even though it has been shown that mechanical overload of the joints can be an important trigger for developing osteoarthritis.[44] Further, excess loading is the primary driver of progression of the OA disease,[27] and it has been shown that these increased loads have a direct relationship to the severity of pain in the joint.[37] Increased loads on the knee are associated with a

higher prevalence of medial-compartment knee OA. They are also associated with a faster rate of disease progression.[27] Arthroscopic surgery of the knee (lavage, debridement, chondroplasty, microfracture) in patients where loading is the primary culprit may only temporarily alleviate symptoms because the biomechanics of the joint are not addressed; thus, the results are not long-lasting and are often considered unacceptable.[45] Thus, even when other therapies are applied, the need to reduce excess loading to enhance the success of those other approaches is important.

Because lower-extremity OA onset and progression are largely mediated by excessive and/or abnormal loading across the joint, technologies that absorb or transfer loads away from the affected compartment(s) have great potential in the treatment of this disabling condition. Altering the loads on an osteoarthritic joint can decrease pain and even increase the radiographic joint space.[27] There is further evidence in the clinical literature that a reduction in knee adduction movement (which is a direct indicator of loads on the knee joint) results in pain relief and improvement in function.[11,31,46–51]

Although there is substantial scientific evidence to support the need for altering joint loading, there is still a need for a less invasive treatment option between medical therapy and severe, joint-altering surgery such as HTO or joint replacement that is effective and durable. The fundamental need is to decrease the loads on the knee joint, which is key to addressing the underlying disease mechanism and has been shown to result in pain relief and improvement in function. If this could be accomplished without having to replace the joint or shift the entire load to another portion of the joint, it is believed that this would be a much more durable and successful route for the patient. Furthermore, delaying the need for arthroplasty reduces the need for future revision surgery, which is costlier and associated with more complications versus first-time procedures.

Characteristics of an ideal treatment method for patients with knee OA unresponsive to conservative measures include a minimally invasive procedure that significantly improves pain and disability and results in biomechanical and/or unloading alterations that may slow OA progression.

In summary, there exists a need for a less invasive alternative that achieves the following:

- Targets the disease process at an early stage to fill the treatment gap between the time when patients no longer respond reasonably well to conservative care and the time when a total joint procedure becomes necessary
- Reduces excess loading on the knee joint
- Does not prevent any future arthroplasty options
- Does not require an extended period of recovery or physical therapy
- Allows full range of motion and thus improved function
- Significantly and effectively reduces pain

D. Purpose of This Study

The primary objective of this pilot study is to collect data on the safety and effectiveness of the KineSpring System in patients with primarily unicompartmental medial knee OA through 24 months postoperative follow-up.

II. METHODS AND DESIGN

A. Study Population

This study is designed as a multi-center prospective, single-arm, pilot study. Up to 8 sites will enroll up to 60 subjects over an approximate 12-month duration. The study population will consist of up to 60 male and female subjects who are between the ages of 25 and 80 years of age, with a diagnosis of medial knee

osteoarthritis (Kellgren Lawrence <4) and overall WOMAC pain score ≥40 (scale 0–100).

Eligible subjects must have failed at least 6 months of conservative treatment prior to study entry. Potential study candidates will be approached for consent prior to any data collection. A screening and enrollment log will be provided to study sites to maintain a record of all screened patients.

Patients with active infection, significant OA in the lateral or patellofemoral compartment, inflammatory joint disease, previous arthroplasty in the target knee, previous joint-modifying surgery in the target knee within 12 months of planned procedure, flexion contracture, pathologic ligament instability, metabolic bone disease (marked bone loss or moderate to severe osteoporosis), or morbid obesity (BMI ≥35) will be excluded.

B. Study Duration

All subjects included in this clinical investigation will return for follow-up visits at 6 weeks and at 3, 6, 12, and 24 months. Evaluation of the primary safety and efficacy endpoints will be completed on all subjects at 24 months. Follow-up will continue for a total of 5 years.

C. Primary Outcome

The outcome measures in this study will include the following:

- Knee Injury Outcome Scores (KOOS), including WOMAC pain, function, and stiffness
- Knee Society Knee and Function Scores
- Knee specific pain as measured with the VAS
- Patient Assessment of Global OA status
- High Arthroplasty Activity Score (HAAS)
- EQ-5D

The success criteria have been established using a "responder analysis" at 24-months postoperatively to define whether the effect is clinically relevant. The responder criteria is based on the Osteoarthritis Research Society International (OARSI) and the Outcome Measures in Rheumatology (OMERACT) committee recommendations, wherein a patient is considered to have clinically important change in OA pain and function with a minimum improvement of 20% compared to baseline measures.[7,52] The responder "success" criteria in this study is based on a threshold value of 20% improvement in both pain and function, which meets the minimal clinically important difference of 20% that is traditionally used to establish responder criteria.

The primary study endpoint is the rate of over all subject success at 24 months. An individual patient will be declared a clinical success if all of the following conditions are met at the 24-month follow-up:

1. Clinically significant improvement of at least 20% from baseline for the WOMAC pain severity subscale with an absolute change of ≥10 points
2. Clinically significant improvement of at least 20% from baseline for the WOMAC function subscale with an absolute change of ≥10 points
3. Maintenance of normal range of motion defined as a) knee flexion range between 90° and 140° and b) knee extension within 10° of the "neutral" or the 0° position
4. No subsequent surgical intervention of the medial compartment of the knee (including device failures requiring removal or revision) and no serious device-related adverse events or device failures
5. Maintenance of device integrity as evaluated by radiographic assessment

D. Follow-Up and Reporting

Subjects will be followed for 5 years, with an option to continue follow-up for a total of 10 years, if required by regulatory authorities. Follow-up visits and examination will occur for all patients at 6 weeks, and at 3, 6, 12, and 24 months post-enrollment to collect data for the primary evaluation of safety and effectiveness with annual follow-up thereafter.

At each follow-up visit, subjects will be interviewed to determine whether adverse events (AEs) were experienced since the previous follow-up visit. A complete orthopedic knee assessment will be performed at baseline for all subjects and again during each follow-up. All subjects will be required to complete KOOS (including WOMAC subscales), knee pain severity score and global assessments, HAAS, and EQ-5D to evaluate, disability, function, pain, and quality of life at each follow-up visit.

Radiographic evaluations will be performed at pre-op, discharge, and at 3, 12, 24, 36, 48, and 60 months for all subjects. MRI evaluations will be performed at the pre-op visit and at the 2-year follow-up.

Subjects requiring explant of the KineSpring System will continue to participate in follow-up through the 24-month primary endpoint. These subjects will take part in all protocol required follow-up examinations, tests, and the completion of questionnaires. For subjects with device failures, data up to the time of explant will be pooled with all other subjects and analyzed on a per protocol basis. All data collected after explant of the KineSpring System will be pooled and analyzed separately from subjects having retained the KineSpring System.

Although all subjects' active participation in the trial will end at 5 years, investigators will be asked to continue to follow all subjects in accordance with standard care and report the long-term survivorship of the implant to the study sponsor through a 10-year follow-up.

E. Statistical Analyses

A subject is considered a responder if he or she is a success regarding each of the four individual primary outcome measures. The 95% confidence interval of the success rate will be calculated for the success rate at 24 months. For continuous variables, the sample size, mean, standard deviation, and range will be calculated. For categorical variables, the number and percentage in each category will be calculated.

F. Safety Outcomes

Safety outcomes will be determined by evaluating by the type, frequency, severity, and relatedness of adverse events through the 5-year time point for all subjects.

G. Baseline Variables

Demographic and baseline variables will be summarized. Sample sizes, means, standard deviations, and ranges will be calculated for all continuous variables.

Baseline predictors of 24-month success rates will be examined using single and multiple logistic regression models. Baseline predictors of 24-month WOMAC pain and function subscale scores will be examined using single and multiple linear regression models.

H. Ethical Aspects

The study has been approved by the appropriate IRBs before the subject enrollment process. Informed consent will be obtained regarding the objective and procedures of the study and possible risks involved. Written informed consent will be obtained from all subjects prior to performing any study procedures in this clinical study.

III. CONCLUSION

This protocol describes the design of a multicenter prospective, single arm, pilot study that will collect data on the safety and effectiveness of the KineSpring in patients with primarily unicompartmental medial knee osteoarthritis through 24 months postoperative follow-up. These data will provide insights on the overall clinical success and safety outcome of KineSpring System.

REFERENCES

1. Altman RD. Overview of osteoarthritis. Am J Med. 1987 Oct 30;83(4B):65–9.
2. Fajardo M, Di Cesare PE. Disease-modifying therapies for osteoarthritis: current status. Drugs Aging. 2005;22(2):141–61.
3. Annual estimates of the population by sex and five-year age groups for the United States: April 1, 2000 to July 1, 2007. Population Division, US Census Bureau. 2008;NC-EST2007-01.
4. United States bone and joint decade: the burden of muskuloskeletal diseases in the United States. Am Acad Orthop Surg. 2008; Rosemont, IL.
5. Felson DT, Nevitt MC, Zhang Y, Aliabadi P, Baumer B, Gale D, Li W, Yu W, Xu L. High prevalence of lateral knee osteoarthritis in Beijing Chinese compared with Framingham Caucasian subjects. Arthritis Rheum. 2002 May;46(5):1217–22.
6. Radin EL, Burr DB, Caterson B, Fyhrie D, Brown TD, Boyd RD. Mechanical determinants of osteoarthrosis. Semin Arthritis Rheum. 1991 Dec;21(3 Suppl 2):12–21.
7. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and cartilage/OARS, Osteoarthritis Research Society. 2008 Feb;16(2):137–62.
8. Superio-Cabuslay E, Ward MM, Lorig KR. Patient education interventions in osteoarthritis and rheumatoid arthritis: a meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. Arthritis Care Res. 1996 Aug;9(4):292–301.
9. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med. 1992 Apr 1;116(7):535–9.
10. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, Ettinger WH, Jr, Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum. 2004 May;50(5):1501–10.
11. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005 Jul;52(7):2026–32.
12. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005 Jul;82(1 Suppl):222S–5S.
13. Ettinger WH, Jr., Burns R, Messier SP, Applegate W, Rejeski WJ, Morgan T, Shumaker S, Berry MJ, O'Toole M, Monu J, Craven T. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. The Fitness Arthritis and Seniors Trial (FAST). JAMA. 1997 Jan 1;277(1): 25–31.
14. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005 Apr;64(4):544–8.
15. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F, Carr A, Chakravarty K, Dickson J, Hay E, Hosie G, Hurley M, Jordan KM, McCarthy C, McMurdo M, Mockett S, O'Reilly S, Peat G, Pendleton A, Richards

S. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee--the MOVE consensus. Rheumatology (Oxford). 2005 Jan;44(1):67–73.

16. Schattner A. Review: both aerobic and home-based quadriceps strengthening exercises reduce pain and disability in knee osteoarthritis. ACP J Club. 2005 Nov-Dec;143(3):71.
17. Bennell KL, Hinman RS, Metcalf BR, Buchbinder R, McConnell J, McColl G, Green S, Crossley KM. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. Ann Rheum Dis. 2005 Jun;64(6):906–12.
18. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. Ann Intern Med. 2000 Feb 1;132(3):173–81.
19. Kirkley A, Webster-Bogaert S, Litchfield R, Amendola A, MacDonald S, McCalden R, Fowler P. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am. 1999 Apr;81(4):539–48.
20. Ortiz E. Market withdrawal of Vioxx: is it time to rethink the use of COX-2 inhibitors? J Manag Care Pharm. 2004 Nov–Dec;10(6):551–4.
21. Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ. 2004 Aug 17;171(4):333–8.
22. Das A, Neher JO, Safranek S. Clinical inquiries. Do hyaluronic acid injections relieve OA knee pain? J Fam Pract. 2009 May;58(5): 281c–e.
23. Hawker GA, Guan J, Croxford R, Coyte PC, Glazier RH, Harvey BJ, Wright JG, Williams JI, Badley EM. A prospective population-based study of the predictors of undergoing total joint arthroplasty. Arthritis Rheum. 2006 Oct;54(10):3212–20.
24. Hawker GA, Wright JG, Badley EM, Coyte PC. Perceptions of, and willingness to consider, total joint arthroplasty in a population-based cohort of individuals with disabling hip and knee arthritis. Arthritis Rheum. 2004 Aug 15;51(4):635–41.
25. Hawker GA, Wright JG, Coyte PC, Williams JI, Harvey B, Glazier R, Wilkins A, Badley EM. Determining the need for hip and knee arthroplasty: the role of clinical severity and patients' preferences. Med Care. 2001 Mar;39(3):206–16.
26. Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, Blair SN, Berman BM, Fries JF, Weinberger M, Lorig KR, Jacobs JJ, Goldberg V. Osteoarthritis: new insights. Part 2: treatment approaches. Ann Intern Med. 2000 Nov 7;133(9):726–37.
27. Andriacchi TP, Lang PL, Alexander EJ, Hurwitz DE. Methods for evaluating the progression of osteoarthritis. J Rehabil Res Dev. 2000 Mar–Apr;37(2):163–70.
28. Cerejo R, Dunlop DD, Cahue S, Channin D, Song J, Sharma L. The influence of alignment on risk of knee osteoarthritis progression according to baseline stage of disease. Arthritis Rheum. 2002 Oct;46(10):2632–6.
29. Erdogan F, Kesmezacar H, Ogut T, Orak M, Tenekecioglu Y. [The use of a modified Weber technique for high tibial osteotomy]. Acta Orthop Traumatol Turc. 2003;37(1): 26–32.
30. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001 Jul 11;286(2):188–95.
31. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee jointloading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007 Oct 15;57(7):1254–60.
32. Gaasbeek RD, Nicolaas L, Rijnberg WJ, van Loon CJ, van Kampen A. Correction accuracy and collateral laxity in open versus closed wedge high tibial osteotomy. A one-year

randomised controlled study. Int Orthop. 2010 Feb;34(2):201–7.

33. Luites JW, Brinkman JM, Wymenga AB, van Heerwaarden RJ. Fixation stability of opening- versus closing-wedge high tibial osteotomy: a randomised clinical trial using radiostereometry. J Bone Joint Surg Br. 2009 Nov;91(11):1459–65.
34. van Raaij TM, Reijman M, Furlan AD, Verhaar JA. Total knee arthroplasty after high tibial osteotomy. A systematic review. BMC Musculoskelet Disord. 2009;10:88.
35. Marwin S. Medial Compartment Arthritis: Treatment. Medscape Today [serial on the Internet]. 2008: Available from: http://emedicine.medscape.com/article/1251851-treatment.
36. Hernigou P, Jaafar A, Hamdadou A. [Leg length changes after upper tibial osteotomy: analysis of different preoperative planning methods]. Rev Chir Orthop Reparatrice Appar Mot. 2002 Feb;88(1):68–73.
37. Tunggal JA, Higgins GA, Waddell JP. Complications of closing wedge high tibial osteotomy. Int Orthop. 2010 Feb;34(2):255–61.
38. Odenbring S, Egund N, Lindstrand A, Lohmander LS, Willen H. Cartilage regeneration after proximal tibial osteotomy for medial gonarthrosis. An arthroscopic, roentgenographic, and histologic study. Clin Orthop Relat Res. 1992 Apr;277:210–6.
39. Wakabayashi S, Akizuki S, Takizawa T, Yasukawa Y. A comparison of the healing potential of fibrillated cartilage versus eburnated bone in osteoarthritic knees after high tibial osteotomy: An arthroscopic study with 1-year follow-up. Arthroscopy. 2002 Mar;18(3):272–8.
40. Amendola A, Panarella L. High tibial osteotomy for the treatment of unicompartmental arthritis of the knee. Orthop Clin North Am. 2005 Oct;36(4):497–504.
41. Maquet P, Radin EL. Osteotomy as an alternative to total hip replacement in young adults. Clin Orthop Relat Res. 1977 Mar–Apr;123:138–42.
42. Intema F, Marijnissen AC, Beekhuizen M, van Roermund PM, bijlsma JW, Lafeber FP. Joint distraction in the treatment of severe knee osteoarthritis; the first results on clinical efficacy and structural repair. EULAR 2008 Annual Congress; Paris. IDE Main: Ann Rheum Dis; 2008. p. 96.
43. W-Dahl A, Robertsson O, Lidgren L. Surgery for knee osteoarthritis in younger patients. Acta Orthop. 2010 Apr;81(2): 161–4.
44. Gunther KP. Surgical approaches for osteoarthritis. Best Pract Res Clin Rheumatol. 2001 Oct;15(4):627–43.
45. Repicci JA, Hartman JF. Minimally invasive unicondylar knee arthroplasty for the treatment of unicompartmental osteoarthritis: an outpatient arthritic bypass procedure. Orthop Clin North Am. 2004 Apr;35(2): 201–16.
46. Chew KT, Lew HL, Date E, Fredericson M. Current evidence and clinical applications of therapeutic knee braces. Am J Phys Med Rehabil. 2007 Aug;86(8):678–86.
47. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage. 2005 Jan;13(1):20–7.
48. Draganich L, Reider B, Rimington T, Piotrowski G, Mallik K, Nasson S. The effectiveness of self-adjustable custom and off-the-shelf bracing in the treatment of varus gonarthrosis. J Bone Joint Surg Am. 2006 Dec;88(12):2645–52.
49. Lindenfeld TN, Hewett TE, Andriacchi TP. Joint loading with valgus bracing in patients with varus gonarthrosis. Clin Orthop Relat Res. 1997 Nov(344):290–7.
50. Pollo FE, Otis JC, Backus SI, Warren RF, Wickiewicz TL. Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. Am J Sports Med. 2002 May–Jun;30(3):414–21.
51. Self BP, Greenwald RM, Pflaster DS. A biomechanical analysis of a medial unloading

brace for osteoarthritis in the knee. Arthritis Care Res. 2000 Aug;13(4):191–7.

52. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004 May; 12(5):389–99.