Osteoarthritis: An Impression and Appropriate Treatment with Allusion to Diacerein

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Abstract

Despite the growing supremacy of OA (Osteoarthritis), many unpredictability exist inhere with its management. Many suggested risk aspects are characterized by extreme loading of vulnerable joint structures. Clinical examination should include an exploration of joint function and the effect of variable risks such as malalignment, muscle strength, and obesity. Braces, footwear, exercises, and starving are given to heighten the scattering of loads on the joints and to diminish the probability that OA and its symptoms will deteriorate. In this conventional methodology, pharmaceuticals of low toxicity are chosen and are specified only when other approaches fail to attain functional improvement. Attention to these issues in dealing with the patient who has OA is acute to lighten the increasing load of OA among older adults. The global analysis of randomized controlled clinical studies and meta-analyses confirmed the usefulness of diacerein in the treatment of knee and hip OA. The use of diacerein is allied with common gastrointestinal syndromes (frequently soft stools and diarrhea), mild skin responses, and unusual hepatobiliary ailments. Recurrent cases of severe diarrhea and occasional cases of potentially serious hepatotoxicity were stated; a risk of cutaneous drug replies could not be excluded. In order to abate this threat, it is suggested to start diacerein management with half the acclaimed dose (50 mg/day) for the first 2–4 weeks, the laxative assets of diacerein being dose-dependent. In the identical perception, starting a management with diacerein is not suggested in patients older than 65 years who are considered to be more exposed to diarrheal difficulties. In equivalent, laxatives should be avoided, and connected treatment with medicines that can lead to hypokalemia should be particularly observed. Lastly, it is practicality to stop treatment as soon as diarrhea follows. To inhibit the threat of hepatotoxicity, diacerein is contra indicated in patients with recent or a history of liver disease and, hence, patients should be screened for major origins of active hepatic disease before starting the treatment. Treatment should be stopped if elevation of hepatic enzymes or supposed signs or symptoms of liver damage are recognized. Diacerein is a compound with an extensive history but whose effects are still not entirely assumed. Further the confirmation of its efficacy in knee and hip OA, there are very few facts on its effect in other OA locations such as the hand, as well as on different types of patient profiles or OA subtypes. Further investigation is also needed to be accomplished to outline the real prospective of diacerein on disease development with well planned, high quality, structure-modifying clinical trials.

Keywords: osteoarthritis; surgical tactics; treatment; risk issues; diacerein.

Introduction

Osteoarthritis (OA) is a developing rampant. Study discloses that in 2000, 25 million people in the U.S and Canada had Osteoarthritis [1, 2]. By 2020, the number of people who have OA will incline to be doubled in large fragment because of the up surging frequency of obesity and the aging of the generation. When OA affect the knee, as it does in about 13% of adults over age 55 years [3], the impact can be fatiguing. Knee OA is the most communal cause of strength vulnerability and affliction. [4]. Despite increasing concern, OA remains an ailing disease, and latest uncertainties about the welfare of several commonly prescribed OA medications have functioned to highlight deficiencies in the traditional medical approach to management.

Current clinical management for OA often is restricted to analgesic medication and vigilant waiting [5] until recommendation for total joint replacement becomes necessary. With few conventional options offered by their doctors, cumulative numbers of older patients are turning to experimental folk remedies and aggressively marketed dietary supplements that have little functional evidence to upkeep their efficacy. There is a great claim for non-pharmacological treatments, and there is a challenging need for physicians to reexamine the current clinical management for OA. This article awards a general outline for the management of the patient who has OA in the form of a narrative review considering diagnosis, examination, and management. It is not wide-ranging (other articles in this issue discuss imaging, weight management, exercise, braces and orthotics, pharmacologic interference, and surgery in more detail); rather, it offers the clinician with an outline of the available treatments. For the concerned clinician further references are provided that can shorten additional reading and, it is predictable, changes in practice [6–11]. The interested clinician has many routes beyond submissive waiting. The authors prerequisite clinicians to be involved intensely in the treatment of patients who have OA and to motivate these patients to run-through self-management tactics that excite more actual long-term treatment of this determined disease.

Classification of OA

1. **Primary OA**-; also known as idiopathic osteoarthritis, this type of OA arises in vast majority of osteoarthritis cases. It is usually diagnosed on the basis of clinical and radiographic imaging findings. The results may be normal at the initial phases of the disease, because cartilage at that time is not directly made up. Eventually, cartilage loss reveals as joint space- narrowing. It is common in elders where there is no earlier pathology. It predominantly happens due to wear and tear changes happening in old stage particularly in weight bearing joints.

2. **Secondary OA-;** It refers to degenerative disease of the synovial joints that results from some predisposing condition, usually trauma, that has adversely altered the articular cartilage and the subchondral bone of affected joints. It is just contrary to primary OA i.e. It transpires in young entities [12–15]. It mainly arises due to an inclining cause such as:
   - Injury to the joint
   - Previous infection
   - Rheumatoid arthritis
   - Congenital dislocation of the hip (CDH)
   - Deformity
   - Obesity
   - Hyperthyroidism

Investigations

1. Blood Tests: Normal
2. Radiological features:
   -Cartilage Loss
   -Subchondral Sclerosis
   -Cysts
   -Osteophytes [16–17]

Clinical Findings:

- In Nodal Generalized OA-

- Observed typically in females of age 40-50yrs.
- Swelling of one or few finger interphalangeal joints
- Immersion of first carpo meta carpal joint is common.
- Pain
- Stiffness
- Susceptibility to OA at other joints specially knees.

- > In Hip OA-
- Often targets superior aspect and less commonly medial aspect of joint.
- Weakness and worsening of muscles
- Pain is extremely deep in groin area
- Pain and limited internal rotation with flexion.

- > In Erosive OA-
- Specially targeting proximal IPJs.
- Common development of IPJ lateral instability.
- Sub-chondral destructions on x-rays
- Ankylosing of IPJs. [18–19].

Table - 1

Differential Diagnosis:-

Features	OSTEOARTHRITIS	Rheumatoid Arthritis	Gout
Manifestation of symptoms affecting the entire body:	Systemic warnings are not prevailing.	Abundant fatigue and a general sensation of being ill are present	Anxieties and a slight fever
Extent of morning stiffness:	Morning stiffness lasts <30-60 mins.	Morning stiffness persists >1hr.	Not seen
Lumps:	Herberden's & Bouchard's nodes	-	-
Aching with Movement:	Movement surges pain.	Movement declines pain.	-
Age of Origination:	Habitually at the age of 50 yrs.	At the age of 20-30 yrs.	In man, after 35yrs. and in females, after menopause
Laboratory investigations:	Ra factor and anti-ccp antibody negative. Usual esr & c-reactive protein.	Ra factor and anti-ccp antibody positive. Esr & c-reactive protein raised.	-

Abbreviations used in the above table:

Ra- Rheumatoid Arthritis
Ccp- Cyclic Citrullinated Peptide
Esr- Erithrocyte Sedimentation Rate

Supplementary forms of arthritis may prevailing with hand, knee, or hip discomfort, including rheumatoid arthritis, psoriatic arthritis, other seronegative spondyloarthropathies (ankylosing spondylitis, arthritis associated with inflammatory bowel disease, reactive arthritis), and sarcoidosis [20–23]. A numeral of other diseases may prejudice a patient to the development of OA, including metabolic diseases (hemochromatosis, Wilson's disease, ochronosis), endocrine diseases (acromegaly, hyperparathyroidism), hypermobility (Ehlers-Danlos syndrome), crystal arthropathy (gout, calcium pyrophosphate dihydrate deposition), neuropathic joints, and chondro dysplasias[24-26].
In addition, patients existent with region pain from other causes. In the regions commonly inflated by OA, other mutual causes for local ache include

1. Hip pain: trochanteric bursitis, iliopsoas tendonitis, quantified pain from lumbosacral spine, avascular necrosis, inguinal hernia, and hip fracture
   [27]
2. Knee pain: pes anserine bursitis, iliotibial band friction syndrome(Runner's knee), patella tendonitis, patella femoral pain syndrome, prepatellar bursitis, and semi membranosous bursitis [28]
3. Hand pain: De Quervain's tenosynovitis, carpal tunnel syndrome (median nerve compression), flexor tenosynovitis (trigger finger), and ulnar nerve compression

These prospects should be measured in the differential analysis when a person appraises of pain in these extents, and both the history taking and physical inspection should be modified to eliminatory

Fig. 1

Management of OA: Pyramidal Tactic
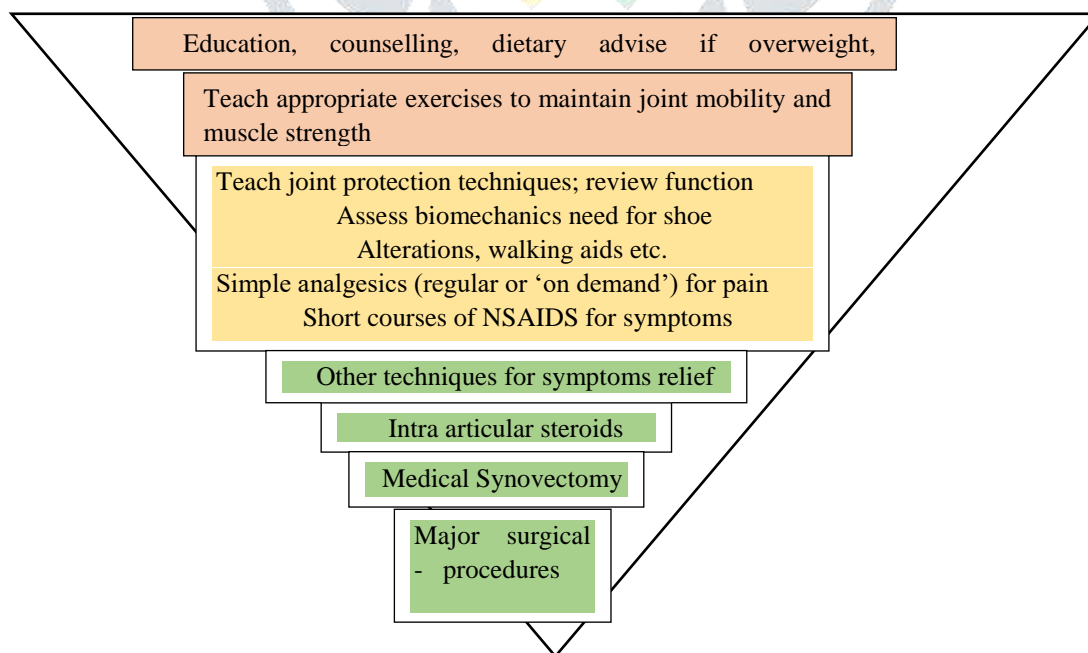
Everyone ⟹ **some patients/ more severe cases** ⟹ **Most severe cases** ⟹

Education, counselling, dietary advise if overweight,

Teach appropriate exercises to maintain joint mobility and muscle strength

Teach joint protection techniques; review function
Assess biomechanics need for shoe
Alterations, walking aids etc.

Simple analgesics (regular or 'on demand') for pain
Short courses of NSAIDS for symptoms

Other techniques for symptoms relief

Intra articular steroids

Medical Synovectomy

Major surgical - procedures

Table – 2

Management of Osteo Arthritis

Objectives in managing of OA	
Education	The patient, relatives & careers should recognize the Ailment & know how to defend themselves
Release symptoms	Pain, difficulty and other symptoms should be measured With least threat to the patients.
Diminish handicap	any significance on function, and any disability or handicap should be reduced through proper rehabilitative technique
Bound progression	Factors expected to worsen the ailment should be eluded.
Difficulties in understanding of controlling intents	
Shortage of understanding of "disability and handicap" in OA	
Deficiency of understanding of "cause and symptoms"	
Failure to control or recognize "disease progression"	

The management of OA comprise of a combination of treatment options. Inappropriately, the devastating majority of treatments tested and used for OA presently are drugs and/or surgery. For example, in one meta-analysis of trials in OA, 60% considered the effect of drug treatment, and 26% estimated surgical procedures [29]. The toxicity/adverse-event summaries of the most commonly used prominent therapies, such as NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors, and total joint replacement are life-threatening when compared with conventional interventions such as exercise, weight loss, braces, and orthotics [6]. Possibilities for the conservative care of patients who have knee OA often are unseen [5]. The authors believe that pharmaceuticals should be manageable only when conservative efforts fail to improve function and that surgical interventions should be a preceding alternative.

In the lack of a cure, current therapeutic modalities are intended mainly at reducing pain and improving joint function by guiding symptom relief and do not abbreviate any improvement in joint structure. The management of OA should be modified so that it conforms to the specific decisions of the clinical examination, especially in patients who are overweight and/or have joint malalignment and muscle faintness. Wide-ranging management always includes a combination of treatment options that are focused toward improving the patient's pain and tolerance for functional activity. Treatment plans never should be well-defined strictly according to the radiographic form of the joint but instead it should remain flexible so that they can be converted according to the functional and symptomatic responses attained.

The endorsed grading of management should consist of non pharmacologic modalities first, then drugs, and then surgery. Too often the first step is forgotten or is not highlighted sufficiently, to the patient's impairment. In addition, combinations of managements are used commonly in clinical practice and may compromise synergistic supports. (Fig. 1).

A number of well-written approaches that define the management of OA established on endorsement from trials and expert settlement are prevailing. [6–9].

The American College of Rheumatology released expert-consensus strategies for the controlling of hip and knee OA in 2000 [8]. These procedures now are fairly obsolete, and the Osteoarthritis Research Society International (OARSI) or European League Against Rheumatism (EULAR) guidelines and approvals should be used in preference.

The EULAR recommendations for managing of knee OA, published in 2003, were acknowledged using an evidence-based medicine and expert belief tactic (Box 1) [6]. These modernized recommendations keep some of the previous offers for the large number of treatment options available for knee OA but also include improved affirmations and new strategies.

Additional Delphi consensus approach guidelines were proven for the management of hip OA in 2005 [7]. Ten key agreements for the treatment of hip OA were established based on research warning and expert agreement. The efficacy and cost effectiveness of these recommendations were assessed and the asset of the recommendations was calculated.

Updated, evidence based, international consensus recommendations for the management of hip and knee OA have been proven by the OARSI Treatment Guidelines Committee [9].

> ➢ **Endorsements for handling knee osteoarthritis** [9].

1. The supreme management of knee OA comprises of a combination of non-Pharmacologic and pharmacologic management modalities.
2. The treatment of knee OA should be modified according to
   (a) Knee risk aspects (obesity, adverse mechanical factors, physical activity)
   (b) General threat elements (age, comorbidity, polypharmacy)
   (c) Level of pain intensity and susceptibility
   (d) Sign of sensitivity (eg. outpouring)
   (e) Location and degree of structural damage
3. Non-pharmacologic treatment of knee OA should comprise regular education, exercise, use of appliances (sticks, insoles, knee bracing), and weight discount.
4. Paracetamol should be the first oral analgesic cast-off and is the preferred long-term oral analgesic.
5. Topical applications (nonsteroidal anti-inflammatory drugs [NSAIDs], capsaicin) have clinical effectiveness and are harmless.
6. NSAIDs should be increased in patients unresponsive to paracetamol. In patients at enlarged gastrointestinal risk, nonselective NSAIDs and effective gastro protective agents, or selective cyclo-oxygenase 2 (COX-2) inhibitors should be used.
7. Opioid analgesics, with or without paracetamol, are helpful alternatives in patients in whom NSAIDs, including COX-2 selective inhibitors, are contraindicated, unproductive, and/or poorly tolerated.
8. Indicative slow-acting drugs in OA (glucosamine sulfate, chondroitin sulfate, avocado-soybean unsaponifiables, diacerein, hyaluronic acid) have characteristic effects and may transform structure.
9. Intra-articular injection of a long-acting corticosteroid is specified for knee pain, particularly if convoyed by effusion.
10. Joint replacement must be restrained in patients who have radiographic suggestion of knee OA and who have persistent pain and disability.

> ➢ **Specialists suggestions for treatment of hip osteoarthritis established through three delphi series**
> ✓ Optimal management of hip OA involves a combination of non-phamacologic and pharmacologic treatment modalities.

1. Treatment of hip OA should be tailored according to-:
   (a) Hip risk aspects (obesity, adverse mechanical factors, physical activity, dysplasia)
   (b) General risk aspects (age, sex, comorbidity, comedication)

(c) Level of pain intensity, infirmity, and handicap

(d) Location and degree of structural impairment

(e) Patient's desires and beliefs

2. Non-pharmacologic treatment of hip OA should include consistent education, exercise, use of appliances (stick, insoles), and weight reduction (if the patient is obese or overweight).

3. Because of its worth and care, paracetamol (up to 4 g/d) is the oral analgesic of first choice for mild or adequate pain and the superlative long-term oral analgesic.

4. Nonsteroidal anti-inflammatory drugs (NSAIDs) at the deepest actual dose should be added or replaced in patients who respond inadequately to paracetamol. In patients, at increased gastrointestinal risk, nonselective NSAIDs plus a gastro protective agent or a selective cyclo-oxygenase 2 (COX-2) inhibitor should be used.

5. Opioid analgesics, with or without paracetamol, are suitable alternatives in patients in whom NSAIDs including COX-2 selective inhibitors are contraindicated, useless, and/or poorly tolerated.

6. Symptomatic slow-acting drugs for OA (glucosamine sulfate, chondroitin sulfate, diacerein, avocado-soybean unsaponifiables, and hyaluronic acid) have a characteristic effect and low toxicity, but effect sizes are small, suitable patients are not well defined, and clinically relevant structure modification and pharmaco economic aspects are not well established.

7. Intra-articular steroid injections (guided by ultrasound or radiography) may be painstaking in patients who have an intensity that is impassive to analgesics and NSAIDs.

8. Osteotomy and joint-preserving surgical procedures should be considered in young adults who have symptomatic hip OA, especially in the presence of dysplasia or varus/valgus deformity.

9. Joint replacement must be considered in male patients who have radiographic indication of hip OA and who have intractable pain and disability.

Evidence for appropriate therapies was completed and published in two parts in late 2007 and early 2008. The first part of the report was a serious evaluation of all existing evidence-based and consent guidelines for the treatment of knee and/or hip OA and a systematic review of the recent research evidence. The additional fragment of the report grants the current OARSI evidence-based, expert-consensus recommendations for the treatment of knee and/or hip OA [9].

Non-pharmacologic approaches

It include patient education, weight loss if patients are obese or overweight, exercise, physical therapy, and the use of braces and orthotics.

Education
Patients should be admired to contribute in self-management ways such as those accompanied by the Arthritis Foundation. The clinician should notify patients regarding the natural history of the disease and deliver resources for social support and instruction on managing skills [30,31].

Weight loss
Overweight and obese patients who have hip and knee OA should be roused to lose weight through a combination of diet and exercise. Weight loss decreases the load on the weight-bearing hips and knees. The Arthritis, Diet, and Activity Promotion trial exposed that diet and exercise leads to largely enlargements in self-reported events of pain and function in older overweight and obese adults who have knee OA [32], even in patients who lost only 5% of their total weight over 18 months.

Exercise
Exercise increases aerobic capacity, muscle forte, and stability and also enables weight loss [32,33]. All persons capable of exercise should be encouraged to contribute in a low-impact aerobic exercise program

(walking, biking, or swimming or other marine exercise). Quadriceps-strengthening exercises have been predictable to lead to improvements in pain and function [34–36].

Table – 3

Physical Therapy

Physical medication and Hydrotherapy in the monitoring of OA
Indications for use
Impairment of joint movement without severe joint devastation
Muscle weakness/ wasting and improbability of joints
Malalignment of joints and/ or abnormal joint use
Severe indications not consoled by other measures
Purposes and role of treatment
Advance the range of joint motion
Expansion the strength of muscles acting on the affected joints, which also advances reliability
Optimize joint biomechanics to preserve/ improve position, and reduce any irregular or
Excess loading of the joints
Relieve pain, stiffness and other indications

Physical therapy as mentioned in (Table-3) comprises of a number of activities to facilitate symptom resolution and improve functional scarcities, including range-of-motion exercise, muscle strengthening, muscle widening, and soft tissue mobilization. Though the results of a current randomized, double-blind, placebo controlled trial found that stable contact with a therapist (sham ultrasound therapy) provided equivalent effect in reducing pain and infirmity, the effects in symptom improvement were large in both groups [37]. It is promising that the sham ultrasound therapy may have provided some treatment (eg, massage).Also, one other randomized, controlled trial that focused more on quadriceps strengthening did show a assistance from physical therapy in knee OA [38]. A randomized, controlled trial also found that taping was valued in the management of pain and infirmity in persons who had knee OA [39], Knee braces and orthodontics because the medial tibiofemoral compartment often is involved, intrusions whose objective is to reestablish the knee to reduce transarticular loading on the medial compartment, such as valgus bracing, sometimes are used clinically. Although for many years it has been known that varying loads in patients who have knee OA is a safe, inexpensive, and effective modality of treatment, few studies have estimated these therapies.[40–43]. For patients who have knee instability, there is evidence that valgus bracing and orthotics move the load away from the medial compartment and, in doing so, may deliver great relief of pain and improvement in function [42–44]. The authors of this article are aware of only two randomized trials of the effectiveness of unloader braces for the behavior of varus knee OA [41,42]. These studies display that wearing a valgus brace gives a clinically significant and rapid improvement in the pain and function of patients who have medial OA of the knee. In both studies pain and functional weakening were condensed by 50%, much greater than seen with typical NSAIDs use.[45,46].

Observational readings have submitted that lateral heel wedges can shorten medial compartmental loading, but two randomized, controlled trials evaluating the use of lateral heel wedges in medial knee OA have not established an improvement in symptom severity [47,48]. Conceptually, however, there may still be significance in using orthotics to restore normal foot anatomy in patients who have foot pathology i.e. hallicus valgus or plano valgus deformities), particularly because all forces that go through the knee and hip pass first through the foot.

Patients who have resolute ambulatory pain from hip or knee OA should consider using a cane in the hand contralateral to the painful joint. A cane lessens the loading force on the joint, and its use is associated with

a decrease in pain in patients who have hip and knee OA [49]. All patients who have knee and hip OA should receive appropriate guidance concerning footwear.

Pharmacologic approaches structure-modifying efficacy has not been established persuasively for any of the prevailing pharmacologic agents,

Table - 4

Surgical techniques used in the management of OA

Procedure	Symptoms
Arthroscopic washout or "tidal irrigation"	Modest to severe symptoms w/o severe radiographic variations, beneficial in diagnosis, mainly used for the knee
Joint debridement	Adequate to severe symptoms, especially mechanical type, w/o progressive loss of articular cartilage
Bony decompression	Rarely used in early osteonecrosis or to relieve severe pain
Osteotomy	Pain relief & repositioning of joints, w/o loss of cartilage
Arthroplasty	Severe symptoms with joint impairment as well

Surgical tactics

Surgery should be counterattacked when symptoms can be managed by other treatment modalities as mentioned in (Table-4). The typical signs for surgery are devastating pain and major restriction of functions such as walking, working, or sleeping. Although this treatment for knee OA has a large effect size [55–57], it is an interfering treatment that has linked risks. If surgical intervention is to be chased, an evidence has shown that patients operated on in low-volume hospitals and/or by low-volume surgeons have worse functional consequences 2 years after total knee replacement than those operated on in high-volume hospitals by high-volume surgeons [58].

Pharmacological Treatments:

Intra articular therapy

Synovial fluid is predominant for the typical joint functioning : it acts both as a lubricant in the course of slow action (e.g. In jogging), and as an elastic shock absorber for the period of rapid action (e.g. In running). It additionally serves as a medium for delivering vitamin, and transmitting cellular signals to articular cartilage. Hyaluronic acid, produced via synoviocytes, fibroblasts and chondrocytes, is the principal

chemical factor of synovial fluid. The native hyaluronic acid has a molecular weight of 4-10 million Daltons, and is present in articular fluid in concentration about 0.35g / 100 ml [59]. It is essential for the viscoelastic properties of the fluid considering that of high viscosity, and has a protecting outcomes on articular cartilage and soft tissue surfaces of joints [60]. In pathological conditions, the concentration and molecular weight of hyaluronic acid are reduced, resulting in synovial fluid of lower elasticity and viscosity : the motives which contribute to the low concentrations of hyaluronic acid are diluitional effects, decreased hyaluronan synthesis and free radical degradation [61]. When viscoelasticity of synovial fluid is decreased, the transmission of mechanical force to cartilage may broaden its susceptibility to damage. Hence, the restoration of the common articular homoeostasis is the reason for hyaluronic acid administration into osteoarthritic joints. Furthermore, being hyaluronic acid a physiological component, it is possibly that it can be deprived of adverse reactions, additionally after repeated administrations.

Therapeutic activities of hyaluronic acid

The direct injection of hyaluronic acid in the joint area permits to reach a proper concentration with low doses, favouring a longer permanence within the joint, and accordingly the therapeutic response.
Hyaluronic acid preparations have a short half - life; therefore, the long term effects cannot completely be attributed to the substitution of molecule itself. The term viscosupplementation means restoration of visco - elastic properties, such as cushioning, lubrication, elasticity [62], while the term biosupplementation is used to indicate the restoration of joint rheology, anti - inflammatory and anti - nociceptive effects, normalization of endogenous hyaluronic acid synthesis, and chondroprotection. These activities explain why the clinical efficacy is maintained for a couple of months [63].

Intra-articular Corticosteroids

Intra-articular corticosteroids is a long-standing treatment for OA, and the primary clinical trial of intra-articular CS in knee osteoarthritis [64]. Corticosteroids have marked anti-inflammatory and immunosuppressive outcomes, besides, CS can expand both relative viscosity and awareness of hyaluronic acid [65] in arthritic knee. Whilst there is a debate on the effective time of intra-articular corticosteroids. In spite of the efficacy and cost-effectiveness of cure modalities for knee osteoarthritis are traditionally debated and instructional materials have changed over time, intra-articular corticosteroids and HA stay long-established therapy for knee osteoarthritis [66]. Among the efficacy and security between intra-articular hyaluronic acid and intra-articular corticosteroids, there still haven't reached a consencus. Osteosteoarthritis Research Society International [67] recommend both intra-articular hyaluronic acid and intra-articular corticosteroids for patients with knee osteoarthritis, even as American institution of Rheumatology [68] and National Institute for health and Care [69] just recommend the usage of intra-articular corticosteroids. Hence, we conduct a meta analysis to examine efficacy and security of intra-articular hyaluronic acid and intra-articular corticosteroids in sufferers with knee osteoarthritis.

Duloxetine

Duloxetine is used to treat depression and anxiety. Furthermore, duloxetine is used to help relieve nerve anguish (peripheral neuropathy) in persons with diabetes or ongoing discomfort as a result of scientific stipulations equivalent to arthritis, chronic again soreness, or fibromyalgia (a condition that causes pain). Duloxetine may just give a boost to your mood, sleep, appetite, and energy level, and lessen anxiousness. It can also lessen the pain due to certain medical conditions. Duloxetine is often called a serotonin-norepinephrine reuptake inhibitor (SNRI). This medication works through helping to restore the steadiness of particular natural substances (serotonin and norepinephrine) in the brain.

Oral analgesics

Acetaminophen-

Acetaminophen (Tylenol® and Panadol®) has both pain-relieving and anti-pyretic activities [70]. Acetaminophen, up to 4 g per day, is the first treatment recommended by ACR, OARSI and EULAR (European League Against Rheumatism) [71] guidelines for cure of mild to moderate OA. A efficient review evaluating 15 RCTs considering acetaminophen in hip or knee OA pain [72] revealed that though beneficial over placebo, acetaminophen was second-rate to NSAID for pain control and reduction of stiffness and swelling. Nonetheless, acetaminophen has a superior safety profile in most studies than NSAIDs. There has been argument regarding cardiovascular (CV) [62], gastrointestinal (GI) [73] and renal [74] toxicities of acetaminophen, with long-lasting use of more than 3 g per day related with similar side effects as NSAIDs. In addition, the combination of acetaminophen and NSAIDs may multiple the risk of GI toxicity [75]. We suggest care be used to ensure patients, particularly older adults, do not exceed safe daily dosages, and use of proton pump inhibitor (PPI) should be considered especially with doses greater than 3 g/day or with combination therapy of acetaminophen and NSAID.

NSAIDs-

NSAIDs treat inflammatory pain and also reduce swelling and joint painfulness. A effectual review of 27 RCTs long-established the advantage of NSAID over acetaminophen for pain relief in OA [75]. In large RCTs, selective COX-2 inhibitors (i.e. celecoxib or Celebrex®) appear to produce pain relief similar to non-selective NSAIDs (i.e. ibuprofen, naproxen and diclofenac) but predictable NSAIDs are connected with higher GI toxicity including ulceration, perforation and bleeding [76, 77]. A meta-analysis of observational studies on a variety of NSAIDs determined celecoxib had the slightest CV toxicity among the selective COX-2 inhibitors, while naproxen, ibuprofen and peroxicam warned lesser CV risk than diclofenec among non-selective agents [78]. Despite side effects, NSAIDs remain an option in patients with OA-related pain due to their deep-rooted efficacy. The high rate of co-morbidities in the elderly confounds their use. The decision to use NSAIDs must be a joint decision between the physician and patient, after discussion of the risks, and with a possible plan for checking side effects and observing blood pressure.

Tramadol

Tramadol is a fragile, atypical opioid analgesic, though it does not have as much abuse potential as other narcotics [79] and tramadol is classified by the USFDA as a schedule IV controlled substance making it more attractive to most patients and practitioners. A meta-analysis inspecting the effects of tramadol on OA pain was allotted in early 2007 [80];eleven RCTs including 1019 patients who received tramadol or tramadol/acetaminophen in compare with placebo or active control (either acetaminophen, diclofenac, or other weak narcotic) were merged. The mean transformation in pain scores preferred treatment with tramadol, but the effect was small (RR 1.34, 95% CI 1.13–1.58). Compared with placebo, tramadol was effective, but the extent of pain relief was similar to acetaminophen. A RCT done in elderly patients showed precision in pain and sleep related results [81]; side effects comprised constipation (27.5%), nausea (23.4%) and dizziness (22.7%). Dizziness is a much more significant issue in the elderly due to the risk of falls. In addition, tramadol can drop seizure threshold [82] when titrated or withdrawn rapidly. Slow-titration of this medication may decrease side effects and develop adequacy in grown-up adults.

Opiates

Narcotic analgesics are often used in considering pain in OA patients, but worries about dependency and toxicities are predominantly annoying in the elderly. A resourceful review of non-tramadol opioids (including morphine, codeine, oxycodone, and oxymorphone and transdermal fentanyl) involved 10 trials and 2268 aspirants [83]. Opioids had a small benefit in pain and function over placebo, though serious adverse effects (AE) and dropouts were more with opioids. No modifications between types or doses of opioids were witnessed. A meta-analysis of 41 RCTs of over 6000 patients with non-cancer associated pain

decided that strong opioids like morphine and oxycodone were superior to acetaminophen and naproxen for pain relief but not for efficient outcomes [84]. 80% of patients incorporated had OA, back pain or rheumatoid arthritis. Use of these agents in combination with standard therapy may badge for decreased dosages, but small assistances may be well-adjusted by high AE rates regulating their use mainly in older adults.

Topical/transdermal agents

Topical and transdermal agents used as adjunctive therapy ideally lessen the rate of systemic side effects, making them noteworthy in elderly populations. Following are three commonly used agents.

Capsaicin

ACR, OARSI and EULAR guidelines all recommend capsacin for handling of pain in OA. Topical capsacin is prevailing over-the-counter in two different assets (0.025% and 0.075%). It has a measured onset of action and can cause local burning which may reduce compliance. In older adults, particular consideration to skin integrity and application technique must be taken to avoid intolerance [84].

Topical NSAIDs

Topical NSAIDs are recommended by OARSI and EULAR guidelines for managing of hand and knee OA. Two meta-analyses covering 14 placebo-controlled RCTs confirmed efficacy of topical NSAIDs with extent of consequence from two to four weeks. In this analysis, heterogeneity of the products studied, adjustable efficacy endpoints, and lack of adequate published studies in large numbers of patients made it puzzling to conclude whether these agents remain efficacious beyond 4 weeks of treatment [85, 86]. In the United States, the FDA approved topical diclofenec sodium 1% (Voltaren gel® and Pennsaid ®) for OA pain management in 2007. A fresh double blinded 8 week RCT [87] demonstrated reduction in pain score by 42–45% in patients >40 years old with primary hand OA cured with diclofenac sodium 1% gel related to placebo. AEs were corresponding to placebo in terms of GI and CV events. Another RCT compared topical diclofenec to oral diclofenec, as well as topical and oral placebos in patients with OA (mean age 61 years) [88]. This study confirmed similar efficacy of topical and oral diclofenac, with a potential shrinkage in GI toxicity paralleled with oral therapy, making it a remarkable choice in older adults. Whether there is also a reduced long-term CV risk with topical compared to oral diclofenac has yet to be resolute. When applied topically, diclofenac plasma concentration is 158 times less than with oral administration (voltaren gel package insert); local irritation arises in 4% of the patients [87].

Transdermal lidocaine patches

Although there are no RCTs testing efficacy, 5% lidocaine transdermal patches (Lidoderm™) are frequently used by clinicians to control pain in OA. Two open-label trials running their use, reporting reduction in knee pain in OA patients after two-weeks [89, 90]. AE are negligible; most common is local skin irritation. Dizziness and headaches have been stated with over-dosage and patients and care-givers must be directed to apply patches only for 12 constant hours within every 24 h period (alternate 12 h on with 12 h off).

Alternative agents/nutraceuticals

There are a number of dietary and herbal supplements that are stated to decrease arthritis pain and upturn mobility. These contain ginger extracts, methyl sulfonyl methane, MSM s-adeno syl methionine (SAM-e), and ASU (Avocado-Soybean Unsaponifiables) [91]. Most of these supplements are tolerant, may have uncertain AE and have not been studied in an appropriately randomized and controlled approach to measure efficacy. An exclusion is glucosamine and chondroitin [92, 93] which is discussed below.

Glucosamine/chondroitin Glucosamine and chondroitin are prevailing in many different formulations. As they are unfettered, the actual content of glucosamine and chondroitin in various commercial products was found to vary from 0% to 115% of the labeled amount [94, 95]. In an efficient review of 15 placebo RCT,

glucosamine sulphate (GS) preparation were marginally effective for pain relief, and no improvement in physical function or stiffness was noted [96]. The Glucosamine/Chondroitin Arthritis Trial (GAIT) was a double blinded, placebo controlled trial which found that glucosamine/chondroitin was not active for OA pain [97]. This trial included more than 1500 patients with knee OA and compared glucosamine hydrochloride (GH), chondroitin sulfate, the combination, and celecoxib. Neither glucosamine nor chondroitin, alone or in combination, demonstrated efficacy by the primary effect of reduction in pain score by 20% at week 24. These results are in contrast to the GUIDE (glucosamine sulfate Unum In die Efficacy) Trial [93] that compared glucosamine sulfate (GS), acetaminophen and placebo, and demonstrated that GS was better than placebo for pain relief. Whether Glucosamine and/or chondroitin are effective in reducing joint damage from OA is controversial, with opposing results from abundant small studies, and considerable publication bias in this area [94]. In addition, these agents can be quite costly, although they seem to be safe so many patients are keen to try these nutraceuticals.

Diacerein

Outline

Diacerein is an symptomatic slow-acting drug in osteoarthritis with anti-inflammatory, anti-catabolic and pro-anabolic assets on cartilage and synovial membrane. It has also lately been shown to have defending effects against subchondral bone remodeling. Constructed on a literature review of clinical trials and meta-analyses, the ESCEO approves that the efficacy of diacerein is alike to that of non-steroidal anti-inflammatory drugs (NSAIDs) after the first month of usage, and pleased to that of paracetamol. Moreover, diacerein has exposed prolonged effect on symptoms of several months once treatment was stopped. The use of diacerein is linked with common gastrointestinal side effects such as soft stools and diarrhea, common mild skin reactions, and, uncommonly, hepatobiliary disorders. However, NSAIDs and paracetamol are well well-known to cause hypothetically severe hepatic, gastrointestinal, renal, cutaneous and cardiovascular reactions. Therefore, the ESCEO defines that the benefit–risk balance of diacerein remains positive in the symptomatic treatment of hip and knee osteoarthritis. Additionally, correspondingly to other SYSADOAs, the ESCEO positions diacerein as a first-line pharmacological background treatment of osteoarthritis, particularly for patients in whom NSAIDs or paracetamol are contraindicated.

The Mechanism of Action of Diacerein in Osteoarthritis

In Vitro Appraisals-, The foremost mechanism of action of diacerein is to obstruct the interleukin-1b (IL-1b) system and related downstream gesturing [98]. Diacerein has been exposed to effect the activation of IL-1b via a reduced production of IL-1 converting enzyme [99], as well as to distress the sensitivity to IL-1 by decreasing IL-1 receptor levels on the cell surface of chondrocytes [100] and by incidentally increasing IL-1 receptor antagonist production [101, 102]. Production of IL-1b may also be overstated, as diacerein has been shown to inhibit the IL-1b-induced activation of transcription factor NF-jB, which fuels pro-inflammatory cytokine expression [103-05]. Downregulation of IL-1 levels has been long recognized in the synovial fluid of patients with knee OA [106].

Moreover its anti-inflammatory assets, diacerein has been shown to have anti-catabolic [104-105] and pro-anabolic effects [106, 107-109] on cartilage and synovial membrane, as well as self-protective effects against subchondral bone remodeling.

Structural effect of Diacerein

Various clinical trails have confirmed the efficacy of diacerein in patients with hip osteoarthritis. In a study conducted to evaluate the effect of diacerein in a patient of hip Osteoarthritis over a 3 year period using progression of joint space narrowing as assessment criteria, it has been found that mean progression of narrowing was significantly less in patients treated with diacerein from 0.18 per year to 0.13 per year at the end of third year. For the first time significant structure modifying effect of diacerein as compared to

placebo was demonstrated in this study (110-111).The effect of the drug in acute exacerbations of osteoarthritis of hip has been documented in approximately 30 studies. It is much superior to that of placebo and over a common NSAID tenoxicam at the 60th treatment day (112). Diacerein has been also shown to be effective in modification of symptoms and structure in patients of Knee OA (113). So there is no limitation on the duration of its use. The optimal daily dose which relief symptoms in osteoarthritis knee calculated from effect on VAS assessment criteria of pain on movement was found to be 100mg/day (113). Diacerein is well tolerated, the predominant adverse effect include transient change in bowel habits (114). It seems neither responsible for gastrointestinal bleeding nor for renal, liver nor hematological toxicities.Non significant discoloration of urine occurs during treatment because of urinary elimination of metabolites of diacerein. No allergic cutaneous reaction were reported in knee osteoarthritis trial (113) .In 3 year hip osteoarthritis trial, rash or pruritis was noted in 3% patients on placebo and in 7% patients on diacerein 100mg daily (115). No severe allergic reaction has been reported till date.

Clinical Figures on the Safety of Diacerein

Gastrointestinal

Concerning the risk of gastrointestinal disorders, the most frequently reported events with diacerein were loose stools or diarrhea. Diarrhea was cited to be generally mild to moderate in all publications that refer to the severity [116-18], and followed in the first 2 weeks of treatment. No particular pattern of associated disorders could be seen. In all cases, the diacerein-induced diarrhea was reversible after termination of treatment. Furthermore, diarrheal symptoms condensed in most cases after continuous treatment [119].

The post-marketing investigation of diacerein revealed that 25 severe cases of diarrhea were stated. Three of them troubled elderly patients, who experienced dehydration and electrolyte disorders; one case was incurable and occurred in a 79-year-old female with a medical history of arterial hypertension and cardiac arrhythmia [120].

Cutaneous

The skin was not a target organ for toxicity in short- and long-term animal toxicology studies. Nevertheless, the frequency of cutaneous events in the 15 published clinical trials estimating diacerein ranged between 1.8 % [121-22] and 9.4 % [123]. The present review identified rash, pruritus and eczema as the most common cutaneous reactions described in clinical trials. They are suitably reflected in the product information with a frequency of [1/100 and \1/10).

Furthermore, the available post-marketing statistics revealed a few severe cases of cutaneous events: four erythema multiform, two Stevens-Johnson syndrome (SJS) and three toxic epidermal necrolysis (TEN) [124].

Hepatic

Amongst the 15 published clinical trials considering diacerein, only Zheng et al. [125] reported the expression of a hepatic adverse event: one treatment disturbance due to increase in hepatic enzymes. The PRAC performed a more complete analysis of available data and retrieved seven clinical trials screening abnormalities of liver tests. These were mostly categorized by mild/moderate liver enzyme increase (ALT, AST \5 ULN) without increases in bilirubin [124].

A summative of 89 cases within the post-marketing surveillance were measured as hepatic reactions. The most numerous reactions were liver function test abnormalities (41 cases) [124]. One case of hepatic failure had a fatal result and a close temporal link with diacerein.

Cardiovascular

Diacerein does not appear to show cardiovascular toxicity. Undeniably, a toxicology reading designed in accordance with ICH S7A guidelines confirmed that diacerein at 5 and 30 mg/kg/day for 7 consecutive days, and at 60 and 200 mg/kg/day for 4 and 3 next days, respectively, did not distress the cardiovascular system in the sensible dose [126]. The doses used in this study were between 3.6 times and about 143 times the much-admired dose in humans (1.4 mg/kg/day based on a 70 kg person). The wide-ranging preclinical animal toxicology figures with diacerein indicated that the liver was not a target organ for toxicity. The mechanism of action of this hepatic toxicity is not completely understood, but an idiosyncratic mechanism is recommended.

Summary

The global affliction of OA is growing because of the prevalence of symptomatic OA in an aging world population, and the lack of symptom-relieving and disease-modifying treatments. New insights into the pathophysiology of OA are clarifying the mechanisms underlying its different clinical aspects, the treatment of which requires a multidisciplinary approach. Education and preventive measures must accompany symptomatic treatment. In the near future, drugs capable of modifying the natural course of the disease will probably be available, but their benefits should be balanced against considerations of side effects, patient preferences, and costs. Many hypothetical risk factors are categorized by excessive loading of susceptible joint structures. Clinical examination should include an analysis of joint function and the impact of modifiable risks such as malalignment, muscle strength, and obesity. Braces, footwear, exercises, and dieting are recommended to enhance the distribution of loads on the joints and to reduce the possibility that OA and its symptoms will worsen. In this conservative approach, pharmaceuticals of low toxicity are desired and are given only when other methods fail to achieve functional improvement. Attention to these factors in managing the patient who has OA is critical to improve the increasing burden of OA among adults. The overall analysis of randomized controlled clinical studies and meta-analyses established the efficacy of diacerein in the symptomatic treatment of knee and hip OA. The use of diacerein is associated with common gastrointestinal disorders (mostly soft stools and diarrhoea), common mild skin reactions, and uncommon hepatobiliary disorders. Frequent cases of severe diarrhoea and rare cases of potentially serious hepatotoxicity were reported; a risk of cutaneous drug reactions could not be excluded. In the same context, starting a treatment with diacerein is not recommended in patients older than 65 years who are considered to be more vulnerable to diarrheal complications . In parallel, laxatives should be avoided, and concomitant treatment with medicines that can lead to hypokalemia should be especially monitored. Finally, it is common sense to stop treatment as soon as diarrhoea occurs. To prevent the risk of hepatotoxicity, diacerein is contraindicated in patients with current or a history of liver disease and, therefore, patients should be screened for major causes of active hepatic disease before starting the treatment. Treatment should be stopped if elevation of hepatic enzymes or suspected signs or symptoms of liver damage are detected. Diacerein is a compound with a long history but whose effects are still not fully understood. Besides the evidence of its efficacy in knee and hip OA, there are very few data on its effect in other OA locations such as the hand, as well as on different types of patient profiles or OA subtypes. Further research also needs to be performed to define the real potential of diacerein on disease progression with well designed, high quality, structure-modifying clinical trials. Then, depending on the outcomes on cartilage and knowing the proven carry-over therapeutic effect of diacerein, one might question whether continuous or intermittent treatment would be the most reasonable.

References

[1] Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States [see comments]. Arthritis Rheum 1998;41(5):778–99.

[2] Badley E, DesMeules M, et al. Arthritis in Canada: an ongoing challenge. Ottawa (Canada): Health Canada; 2003.

[3] Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am 2004;42(1):1–9.

[4] Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Public Health 1994; 84(3):351–8.

[5] Glazier RH, Dalby DM, Badley EM, et al. Management of common musco skeletal problems: a survey of Ontario primary care physicians [see comment]. CMAJ 1998; 158(8):1037–40.

[6] Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62(12):1145–55.

[7] Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005; 64(5):669–81.

[8] American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000; 43(9):1905–15.

[9] Zhang W, Moskovitz R, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16 (2):137–62.

[10] Hunter D. In the clinic. Osteoarthritis. Ann Intern Med 2007; 147(3):ITC1–8.

[11] Hunter D, Felson D, et al. Osteoarthritis. BMJ 2006; 332(7542):639–42.

[12] Altman R, Asch E, Bloch D. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29(8):1039–49.

[13] Peat G, McCarney R, Croft P, et al. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. AnnRheumDis2001; 60(2):91–7.

[14] Hill CL, Gale DG, Chaisson CE, et al. Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. J Rheumatol 2001; 28(6):1330–7.

[15] Dieppe PA, Lohmander LS, et al. Pathogenesis and management of pain in osteoarthritis. Lancet 2005; 365(9463):965–73.

[16] Witonski D, Wagrowska-Danilewicz M, Raczynska-Witonska G, et al. Distribution of substance P nerve fibers in osteoarthritis knee joint. Pol J Pathol 2005; 56(4):203–6.

[17] Wojtys EM, Beaman DN, Glover RA, et al. Innervation of the human knee joint by substance-P fibers. Arthroscopy 1990; 6(4):254–63.

[18] Benedek TG, Benedek TG, et al. A history of the understanding of cartilage. Osteoarthritis Cartilage 2006; 14(3):203–9.

[19] Freeman MA, Wyke B, et al. The innervation of the knee joint. An anatomical and histological study in the cat. J Anat 1967;101(Pt 3):505–32.

[20] Marshall KW, Theriault E, Homonko DA, et al. Distribution of substance P and calcitonin gene related peptide immune reactivity in the normal feline knee. J Rheumatol 1994; 21(5): 883–9.

[21] Hunter DJ, Zhang YQ, Tu X, et al. Change in joint space width: hyaline articular cartilage loss or alteration in meniscus? Arthritis Rheum 2006; 54(8):2488–95.

[22] Altman RD. Classification of disease: osteoarthritis. Semin Arthritis Rheum 1991; 20 (6 Suppl. 2):40–7.

[23] Hannan MT, Felson DT, Pincus T, et al. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000; 27(6):1513–17.

[24] Bhattacharya T, Gale D, Dewire P, et al. The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee [comment]. J Bone Joint Surg Am 2003; 85- A (1):4–9.

[25] Englund M, Lohmander LS, et al. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Arthritis Rheum 2004; 50(9):2811–9.

[26] Roos EM, Ostenberg A, Roos H, et al. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. Osteoarthritis Cartilage 2001; 9(4):316–24.

[27] Zacher J, Gursche A. Regional musculoskeletal conditions: 'hip' pain. Best Pract Res Clin Rheumatol 2003; 17(1):71–85.

[28] Calmbach WL, Hutchens M, et al. Evaluation of patients presenting with knee pain: part II. Differential diagnosis. Am Fam Physician 2003; 68(5):917–22.

[29] Tallon D, Chard J, Dieppe P, et al. Relation between agendas of the research community and the research consumer. Lancet 2000; 355(9220):2037–40.

[30] Cabuslay E, WardMM, Lorig KR, et al. Patient education interventions in osteoarthritis and rheumatoid arthritis: a meta-analytic comparison with nonsteroidal anti inflammatory drug treatment. Arthritis Care Res 1996; 9(4):292–301.

[31] Marks R, Allegrante JP, Lorig K, et al. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part I). Health Promot Pract 2005; 6(1):37–43.

[32] Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004; 50(5):1501–10.

[33] Ettinger WHJ, Burns R, Messier SP, et al. 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) [see comments]. J Am Med Assoc 1997; 277(1):25–31.

[34] Roddy E, Zhang W, Doherty M, et al. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review [see comment]. Ann Rheum Dis 2005; 64(4):544–8.

[35] Roddy E, Zhang W, Doherty M, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee MOVE consensus. Rheumatology 2005; 44(1):67–73.

[36] Schattner A. Review: both aerobic and home-based quadriceps strengthening exercises reduce pain and disability in knee osteoarthritis. ACP J Club 2005; v143(3):71.

[37] Bennell KL, Hinman RS, Metcalf BR, et al. Efficacy of physiotherapy management of knee joint osteoarthritis: a randomised, double blind, placebo controlled trial. Ann Rheum Dis 2005; 64(6):906–12.

[38] Deyle GD, Henderson NE, Matekel RL, et al. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. Ann Intern Med 2000;132(3):173–81.

[39] Hinman RS, Crossley KM, McConnell J. Efficacy of knee tape in the management of osteoarthritis of the knee: blinded randomised controlled trial. BMJ 2003; 327(7407):135–41.

[40] Hillstrom H, Mcguire J, Whitney K, et al. Immediate effects of conservative realignment therapies of varus knee osteoarthritis. Arthritis Rheum 1998.

[41] Horlick S, Loomer R, et al. Valgus knee bracing form edialgonarthrosis.ClinJSportMed1993; 3: 251–5.

[42] Kirkley A, Webster-Bogaert S, Litchfield R, et al. The effect of bracing on varus gonarthrosis. J Bone Joint Surg Am 1999; 81(4):539–48.

[43] Draper ER, Cable JM, Sanchez-Ballester J, et al. Improvement in function after valgus bracing of the knee. An analysis of gait symmetry. J Bone Joint Surg Br 2000; 82(7):1001–5.

[44] Pollo FE, Otis JC, Backus SI, et al. Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. Am J Sports Med 2002; 30(3):414–21.

[45] Brouwer R, Jakma T, Verhagen A, et al. Braces and orthoses for treating osteo arthritis of the knee. Cochrane Database Syst Rev 2005; 2:2005.

[46] Todd PA, Clissold SP. Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. Drugs 1990; 40(1):91–137.

[47] Maillefert JF, Hudry C, Baron G, et al. Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a prospective randomized controlled study. Osteoarthritis Cartilage 2001; 9(8):738–45.

[48] Baker K, Goggins J, Xie H, et al. A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. Arthritis Rheum 2007; 56(4):1198–203.

[49] Neumann DA. Biomechanical analysis of selected principles of hip joint protection. Arthritis Care Res 1989; 2(4):146–55.

[50] Lo GH, LaValley M, McAlindon T, et al. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis [see comment]. Ann Intern Med 2003; 290(23):3115–21.

[51] Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006; 354(8):795–808. [52] Ortiz E. Market withdrawal of Vioxx: is it time to rethink the use of COX-2 inhibitors? J Manag Care Pharm 2004; 10(6):551–4.

[52] Bookman AA, Williams KS, Shainhouse JZ, et al. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ 2004; 171(4):333–38.

[53] Lin J, Zhang W, Jones A, et al. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomized controlled trials. BMJ 2004; 329(7461):324.

[54] Liang MH, Larson MG, Cullen KE, et al. Comparative measurement efficiency and sensitivity of five health status instruments for arthritis research. Arthritis Rheum1985;28(5):542–47.

[55] Roos E, Nilsdotter A, Toksvig-Larsen S. Patient expectations suggest additional outcomes in total knee replacement [abstract]. Arthritis Rheum 2002; 46(Suppl):9.

[56] Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1977.

[57] Katz JN, Mahomed NN, Baron JA, et al. Association of hospital and surgeon procedure volume with patient-centered outcomes of total knee replacement in a population-based cohort of patients age 65 years and older. Arthritis Rheum 2007; 56(2):568–74.

[58] Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther. 2005;12: 46–55.

[59] Weiss, C. & Band, P. (1995). Musculoskeletal applications of hyaluronan and hylan. Potential uses in the foot and ankle. *Clin Podiatr Med Surg,* Vol.12, No.3, pp. 497-517.

[60] O'Regan, M., Martini, I., Crescenzi, F., De Luca, C. & Lansing, M. (1994). Molecular mechanisms and genetics of hyaluronan biosynthesis. *Int J Biol Macromol,* Vol.16, No.6, pp. 283-286.

[61] Van den Bekerom, MP., Mylle, G., Rys, B. & Mulier, M. (2006). Viscosupplementation in symptomatic severe hip osteoarthritis: a review of the literature and report on 60 patients. Acta Orthop Belg, Vol. 72, No.5, pp. 560-568.

[62] Kikuchi, T., Yamada, H. & Fujikawa, K. (2001). Effects of high molecular weight hyaluronan on the distribution and movement of proteoglycan around chondrocytes cultured in alginate beads. Osteoarthritis Cartilage, Vol.9, No.4, pg. 351-356.

[63] Gigante, A. & Callegari, L. (2011). The role of intra-articular hyaluronan (Sinovial) in the treatment of osteoarthritis. *Rheumatol Int,* Vol. 31, No.4, pp. 427-444.

[64] P. Juni, R. Hari, A.W. Rutjes, R. Fischer, M.G. Silletta, S. Reichenbach, et al., Intra-articular corticosteroid for knee osteoarthritis, Cochrane Database Syst. Rev. (10) (2015) Cd005328.

[65] R.A. Jessar, M.A. Ganzell, C. Ragan, The action of hydrocortisone in synovial inflammation, J. Clin. Invest. 32 (6) (1953) 480e482.

[66] K.M. Koenig, K.L. Ong, E.C. Lau, T.P. Vail, D.J. Berry, H.E. Rubash, et al., The use of hyaluronic acid and corticosteroid injections among medicare patients with knee osteoarthritis, J. Arthroplasty 31 (2) (2016) 351e355.

[67] T.E. McAlindon, R.R. Bannuru, M.C. Sullivan, N.K. Arden, F. Berenbaum, S.M. Bierma-Zeinstra, et al., OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and cartilage/OARS, Osteoarthr. Res. Soc. 22 (3) (2014) 363e388.

[68] M.C. Hochberg, R.D. Altman, K.T. April, M. Benkhalti, G. Guyatt, J. McGowan, et al., American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, Arthritis Care Res. 64 (4) (2012) 465e474.

[69] NICE, Osteoarthritis: Care and Management in Adults, 2014. Clinical guideline CG177 Methods, evidence and recommendations.

[70] Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence base approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) Ann Rheum Dis. 2003; 62:1145–55.

[71] Towheed TE, Maxwell L, Judd MG, et al.: Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006; CD004257.

[72] Chan AT, Manson JE, Albert CM, et al. Nonsteroidal anti inflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006; 113:1578–87.

[73] Rahme E, Barkun A, Nedjar H, et al. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 2008;103: 872–882.

[74] Curhan GC, Knight EL, Rosner B. Lifetime nonnarcotic analgesic use and decline in renal function in women. Arch Intern Med. 2004; 164:1519–24.

[75] Bjordal JM, Klovning A, Ljunggren AE, et al. Short-term efficacy of pharmaco therapeutic interventions in osteoarthritic knee pain: a meta-analysis of randomized placebo-controlled trials. Eur J Pain. 2007; 11:125–38.

[76] McGettigan P, Henry D, et al. Cardiovascular risk and inhibition of cyclo-oxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclo- oxygenase 2. JAMA. 2006; 296:1633–44.

[77] Geba GP, Weaver AL, Polis AB, Dixon ME, et al. Vioxx, Acetaminophen, Celecoxib Trial (VACT) Group: efficacy of rofecoxib, celecoxib and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA. 2002; 287:64–71.

[78] Rahme E, Barkun AN, Toubouti Y, et al. Do proton-pump inhibitors confer additional gastrointestinal protection in patients given celecoxib? Arthrit Care Res. 2007; 57:748–55.

[79] Barkin RL. Extended-release tramadol (ULTRAM ER): a pharmacotherapeutic, pharmacokinetic, and pharmaco dynamic focus on effectiveness and safety in patients with chronic/persistent pain. Am J Ther. 2008; 15:157–66.

[80] Cepeda MS, Camargo F, Zea C, et al. Tramadol for osteoarthritis: a systematic review and meta analysis. J Rheumatol. 2007; 34: 543 –55.

[81] Vorsanger G, Xiang J, Jordan D, et al. Post analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. Clin Ther 2007; (29 Suppl.) : 2520–2535.

[82] Sansone RA, Sansone LA, et al. Tramadol: Seizures, serotonin syndrome, and co administered antidepressants. Psychiatry (Edgmont) 2009; 6: 17–21.

[83] Nuesch E, Rutjes AW, Husni E, et al. : Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev 2009; 4: CD003115.

[84] Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic non cancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006; 174:1589–94.

[85] Lin J, Zhang W, Jones A, et al. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomized controlled trials. BMJ. 2004; 329:324.

[86] Biswal S, Medhi B, Pandhi P, et al. Longterm efficacy of topical nonsteroidal anti-inflammatory drugs in knee osteoarthritis: meta-analysis of randomized placebo controlled clinical trials. J Rheumatol. 2006; 33: 1841–44.

[87] Altman RD, Dreiser RL, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol 2009; 36: 1991–1999.

[88] Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. Pain. 2009; 143: 238–45.

[89] Bellamy N, Campbell J, Robinson V, et al. Intra articular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006; 2: CD005328.

[90] Micu MC, Bogdan GD, Fodor D, et al. Steroid injection for hip osteoarthritis Rheumatology (Oxford) 2010; 49: 1490–94.

[91] Ernst E. Complementary or alternative therapies for osteoarthritis. Nat Clin Pract Rheumatol. 2006; 2: 74–80.

[92] Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006; 354: 795–808.

[93] Herrero-Beaumont G, Ivorra JA, Carmen Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum. 2007; 56: 555–567.

[94] Biggee BA, Blinn CM, McAlindon TE, et al. Low levels of human serum glucosamine after ingestion of glucosamine sulphate relative to capability for peripheral effectiveness. Ann Rheum Dis. 2006; 65: 222–26.

[95] Sun BH, Wu CW, Kalunian KC, et al. New developments in osteoarthritis. Rheum Dis Clin North Am. 2007; 33: 135–48.

[96] Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005; CD002946.

[97] Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis 2010; 69: 1459–1464.

[98] Martel-Pelletier J, Pelletier JP, et al. Effects of diacerein at the molecular level in the osteoarthritis disease process. 2010; 2(2): 95–104.

[99] Moldovan F, Pelletier JP, Jolicoeur FC, Cloutier JM, MartelPelletier J. Diacerhein and rhein reduce the ICE-induced IL-1 beta and IL-18 activation in human osteoarthritic cartilage. Osteoarthr Cartil. 2000; 8: 186–96.

[100] Martel-Pelletier J, Mineau F, Jolicoeur FC, Cloutier JM, Pelletier JP, et al. In vitro effects of diacerhein and rhein on interleukin 1 and tumor necrosis factor-alpha systems in human osteoarthritic synovium and chondrocytes. J Rheumatol. 1998; 25(4): 753–62.

[101] Pelletier JP, Mineau F, Ranger P, Tardif G, Martel-Pelletier J, et al. The increased synthesis of inducible nitric oxide inhibits IL-1ra synthesis by human articular chondrocytes: possible role in osteoarthritic cartilage degradation. Osteoarthr Cartil. 1996; 4(1): 77–84.

[102]   Yaron M, Shirazi I, Yaron I, et al. Anti-interleukin-1 effects of diacerein and rhein in human osteoarthritic synovial tissue and cartilage cultures. Osteoarthr Cartil. 1999; 7(3): 272–80.

[103]   Barnes PJ, Karin M, et al. Nuclear factor-kappa B: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. 1997; 336(15): 1066–71.

[104]   Martin G, Bogdanowicz P, Domagala F, Ficheux H, Pujol JP, et al. Rheininhibits interleukin-1 beta-induced activation of MEK/ERK pathway and DNA binding of NF-kappaB and AP-1 in chondrocytes cultured in hypoxia: a potential mechanism for its disease-modifying effect in osteoarthritis. Inflammation. 2003; 27(4): 233–46.

[105]   Ferreira Mendes A, Caramona MM, de Carvalho AP, Lopes MC, et al. Diacerein prevent interleukin-1 beta-induced nuclear factor-kappa B activation by inhibiting the degradation of inhibitor kappa B-alpha. Pharmacol Toxicol. 2002; 91(1): 22–28.

[106]   Mathieu P. L'interleukine 1: [Interleukin 1 its role, quantitative determination and the difficulties in studying its role in osteoarthritis. Results of a 'pilot' study with diacerein (ART 50) in knee osteoarthritis]. Rev Prat. 1999; 49(Suppl.13): S15–8. French.

[107]   Felisaz N, Boumediene K, Ghayor C, Herrouin JF, Bogdanowicz P, Galerra P, et al. Stimulating effect of diacerein on TGF beta 1 and beta 2 expression in articular chondrocytes cultured with and without interleukin-1. Osteoarthr Cartil. 1999; 7(3):255–64.

[108]   Sanchez C, Mathy-Hartert M, Deberg MA, Ficheux H, Reginster JY, Henrotin YE, et al. Effects of rhein on human articular chondrocytes in alginate beads. Biochem Pharmacol. 2003; 65(3):377–88.

[109]   Schongen RN, Giannetti BM, Van de Leur E, Reinards R, Greiling H, et al. Effect of di acetyl rhein on the phagocytosis of poly morpho nuclear leucocytes and its influence on the biosynthesis of hyaluronate in synovial cells.1988; 38(I)(5): 744–48.

[110]   R.A. Jessar, M.A. Ganzell, C. Ragan, The action of hydrocortisone in synovial inflammation, J. Clin. Invest. 32 (6) (1953) 480e482.

[111]   K.M. Koenig, K.L. Ong, E.C. Lau, T.P. Vail, D.J. Berry, H.E. Rubash, et al., The use of hyaluronic acid and corticosteroid injections among medicare patients with knee osteoarthritis, J. Arthroplasty 31 (2) (2016) 351e355.

[112]   T.E. McAlindon, R.R. Bannuru, M.C. Sullivan, N.K. Arden, F. Berenbaum, S.M. Bierma-Zeinstra, et al., OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and cartilage/OARS, Osteoarthr. Res. Soc. 22 (3) (2014) 363e388.

[113]   M.C. Hochberg, R.D. Altman, K.T. April, M. Benkhalti, G. Guyatt, J. McGowan, et al., American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, Arthritis Care Res. 64 (4) (2012) 465e474.

[114]   NICE, Osteoarthritis: Care and Management in Adults, 2014. Clinical guideline CG177 Methods, evidence and recommendations.

[115]   Delcambre B, Taccoen A. Etude d'ART 50 en pratique rhumatologique quotidienne [Study of ART 50 in daily rheumatological practice]. Rev Prat. 1996; 46(6 Spec No): S49–S52. French.

[116]   Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E,Lequesne M, et al. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Arthritis Rheum. 2001; 44(11): 2539–47.

[117]   Pavelka K, Trc T, Karpas K, Vitek P, Sedlackova M, VlasakovaV, et al. The efficacy and safety of diacerein in the treatment of painful osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled study with primary end points at two months after the end of a three-month treatment period. Arthritis Rheum. 2007; 56(12): 4055–64.

[118]   Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF,Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multi parameter prospective study. Arthritis Rheum. 2001; 44(8):1736–43.

[119]   EMA. European Medicines Agency, Assessment report for diacerein containing medicinal products. 2014 Aug 28.

[120]   Fagnani F, Bouvenot G, Valat JP, Bardin T, Berdah L, Lafuma A, et al. Medico-economic analysis of diacerein with or without standard therapy in the treatment of osteoarthritis. Pharmaco economics. 1998; 13(1 Pt 2):135–46.

[121]   Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L,Dougados M, et al. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. Ann Rheum Dis. 2004; 63(12):1611–17.

[122]   EMA. European Medicines Agency, Assessment report for diacerein containing medicinal products. 2014 Aug 28.

[123]   Zheng WJ, Tang FL, Li J, Zhang FC, Li ZG, Su Y, et al. Efficacy and safety of diacerein in osteoarthritis of the knee: a randomized, multicenter, double-dummy, diclofenac-controlled trial in China. APLAR J Rheumatol. 2006; 9(1): 64–69.

[124]   Renan X, Lepage M, Connan D, Carlhant D, Riche C, Verger P, et al. [Case report of fatal hepatitis from diacerein].The´rapie. 2001; 56(2):190–1. French, 2001; 56: 637–6

[125]   Mattei E, Marzoli GA, Oberto G, Brunetti MM. Diacerein effects on the cardiovascular function of the conscious dog following repeated oral administration [study report]. Rome (Italy): RTC Research Toxicology Centre; 2009.

[126]   Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, et al. Efficacy and safety of diacerein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum. 2000; 43(10): 2339–2348.