

Nutraceuticals and chondroprotective agents for the treatment of osteoarthritis: a narrative review. A controversial resource in the treatment of osteoarthritis

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There are many dietary supplements, chondroprotective agents, disease-modifying agents and nutraceuticals that have been developed and promoted for treating patients affected by osteoarthritis (OA). They can be, and often are, marketed without undergoing a rigorous scientific evaluation. In the literature several *in vitro*- or *in vivo*-trials concerning these compounds can be found, but there is a lack of high-quality, long-term, prospective, comparative studies able to demonstrate unequivocally their effectiveness in the treatment of OA. This is a narrative review concerning the commonest chondroprotective agents found on the market, and assesses whether, on the basis of the current literature, these agents may have a role in the treatment of OA.

KEY WORDS: Osteoarthritis - Cartilage - Arthritis - Glucosamine - Vitamin D - Vitamin C.

Osteoarthritis (OA) is the most common form of degenerative joint disease in developed countries, making it the biggest cause of physical disability in the older population.¹ Moreover, its prevalence is expected to rise as the population ages, creating a substantial burden on primary and secondary care services with elevated costs for National Health Services.^{2, 3} Thus, OA represents a major concern for health-care providers.

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Current pharmacological therapy for OA consists mainly of non-steroidal anti-inflammatory drugs and analgesics, which, although mildly effective, often cause serious adverse events – in particular in the elderly and do not remedy the underlying cartilage damage.⁴ Therefore, these drugs should be used at the lowest effective dose, and if possible, avoided for long-term use.⁵ For these reasons, the investigation and development of new treatments, that can improve the clinical symptoms, with better tolerability and safety, and that also can slow the progression of OA, would be highly desirable.

Over the last few years many compounds labelled as “chondroprotective” agents have been introduced onto the market, mostly as dietary supplements. Technically, the term “chondroprotector” refers to a substance that preserves the articular cartilage during the course of degenerative joint disorders. If these substances are able to demonstrate an alteration in the course of the disease, they may be termed “disease-modifying OA drugs” (DMOADs). DMOADs target not only joint cartilage but also inflammatory pathways and subchondral bone. Thus, their ultimate purpose is to retard the de-

velopment of OA. Despite a considerable effort from pharmaceutical companies to develop several new DMOADs, the guidelines published in 2008 by the Osteoarthritis Research Society International (OARSI) highlighted only glucosamine sulphate (GS) and chondroitin sulphate (CS) as possible DMOADs for the treatment of knee OA, and diacerein for hip OA.⁶ Guidelines by the American College of Rheumatology (ACR) published in 2012 do not recommend any DMOADs for the treatment of OA, implying that there is no conclusive evidence for their efficacy.⁷

Given the lack of clarity on this issue, we present a review of the current literature, analysing both the *in vivo* and *in vitro* evidence, regarding the effect of DMOADs on disease progression in OA.

Materials and methods

A literature search was performed on publications reporting disease-modifying osteoarthritis drugs. The primary medical search engine used for the study was the PubMed database, and all publications that were produced between 1990 and 2013 were included. Search terms such as each compound's name in association with "ar-

thritis", "osteoarthritis", "degenerative arthritis", "chondroprotective" or "cartilage" were used in differing combinations. Combination, truncation and explode functions were used to give the search greater depth. Manual searches of the bibliographies of highlighted papers supplemented database searches. Also, abstracts were screened manually and excluded if they were not relevant to disease modification drugs for OA *in vitro*, *in vivo*, or in patient trials. The primary inclusion criterion was randomised, double-blind, placebo controlled trials reporting the use of DMOADs in the treatment of OA (Level 1 studies). If this criterion could not be satisfied, we considered the publications with the next best level of evidence. We used the same strategy to identify systematic reviews and meta-analyses. There were no language restrictions on articles for inclusion. The results of our search are given in Table I.⁸⁻⁸¹

Results

Glucosamine and chondroitin sulfate

Glucosamine is one of the most frequently-used chondroprotective agents in the treatment of OA. It is an amino-sugar,

TABLE I.—*Results of the search.*

Agent	Papers identified
Glucosamine, chondroitin sulphate, glucosamine/ chondroitin sulphate combined	11 randomised, double-blind, placebo-controlled trials ^{13, 15-18, 20-24, 27} 6 systematic review/metanalyses ^{8, 11, 14, 19, 25, 26} 4 observational studies ^{30, 31, 33, 34} 2 randomised studies ^{37, 41} 2 cross-sectional studies ^{38, 40} 2 longitudinal cohort studies ^{32, 42} 1 review ³⁶ 1 metanalysis ³⁵
Vitamin D	
Vitamin C	1 cross-sectional cohort study ⁵⁰ 2 longitudinal cohort studies ^{49, 54} 1 review ⁵³ 2 animal-model trials ^{47, 48}
Boswellia Serrata Extract	4 randomised, double-blind, placebo-controlled trials ⁵⁷⁻⁶⁰
Manganese	2 randomised, placebo-controlled studies ^{15, 61} 1 animal-model trial ⁶² 2 <i>in-vitro</i> trials ^{63, 64}
Hyaluronic acid	4 randomised, double-blind, placebo-controlled studies ⁶⁶⁻⁶⁹
Diacerein	8 randomised, double-blind, placebo-controlled studies ^{73-75, 77-80, 82} 3 metanalyses ^{70, 76, 81}

required for the synthesis of many macromolecules involved in the homeostasis of cartilage, such as glycoproteins, glycolipids, proteoglycans, glycosaminoglycans (GAGs) and hyaluronic acid.⁸ It is available in several forms, the most common being glucosamine sulfate (GS) and glucosamine hydrochloride (GH).⁹ There is some evidence in the Literature that GS, compared with other glucosamine formulations, is more effective and safer for the treatment of OA.^{10, 11}

Chondroitin sulfate (CS) is an endogenous glycosaminoglycan (GAG) that enables the cartilage to absorb an high amount of water, helping to sustain compressive forces during the joint loop.⁸ Commercially, glucosamine and CS are frequently combined with each other, or with additional agents, although single-ingredient glucosamine and CS preparations may be found.⁹

Relatively little is known about the specific mechanisms of action of glucosamine and CS. Several *in vitro* studies have hypothesised that glucosamine and CS could be involved in the homeostasis of cartilage, both enhancing the synthesis of glycoproteins, glycolipids, glycosaminoglycans (GAGs) in the case of glucosamine, and proteoglycans and hyaluronic acid in the case of glucosamine and CS combined.¹² They may also suppress the production of several pro-inflammatory enzymes, such as TNF- α , nitric oxide, metallo-matrix proteinases (MMPs), cyclooxygenase (COX), phospholipase A2, prostaglandin E2 and IL-8.¹² CS may also reduce the IL-1-induced nuclear factor-B (IL-1-NF-kB), which seems to play a key role in the transcription of many pro-inflammatory genes supposedly involved in OA.¹²

Glucosamine and CS are marketed as dietary supplements. They are slowly and partially absorbed in the gastrointestinal tract and their bioavailability is approximately 20% for glucosamine and 15-24% for CS.¹² Most of the clinical trials refer to Clegg *et al.*, who suggest the dosage of 1200 mg/day for CS and 1500 mg/day for glucosamine,¹³ but significant variability exists and strong evidence is lacking. The low bioavailability of

these products, in particular, may make the standard dosage lower than is required.¹³

There are several clinical studies that analyse the effectiveness and the safety of glucosamine and CS - alone or in combination - however, the research is of variable quality and with conflicting results. McAlindon *et al.*, in a meta-analysis published in 2000, found a wide disparity regarding the effects of glucosamine and CS in the treatment of OA.¹⁴ The authors of this meta-analysis expressed concern about the research quality and the risk of publication bias, proposing that some results could possibly have been exaggerated. Nevertheless, they concluded that a certain degree of efficacy appeared probable for these preparations.

A combination of GH, CS and Mn-ascorbate was found to be effective in patients with mild-to-moderate knee OA compared to a placebo, but it was not effective in patients with radiographically severe knee OA.¹⁵ There was a 17% incidence of mild adverse events (in particular gastrointestinal upset), compared with 19% in the placebo group.

The efficacy of GS in preventing joint space narrowing was studied in a group of 106 patients who received GS for 3 years.¹⁶ The results showed a protective role of GS with a lesser joint space narrowing (mean 0.06 mm), compared with the control/placebo group (mean 0.31 mm). The Western Ontario and McMaster Universities Arthritis Index (WOMAC) score was slightly worse in the placebo group, whereas in the study group it improved. A notably high prevalence of mild, gastrointestinal tract complications was reported in both groups. Similar results were reported by Pavelkà *et al.* in a 3-year, randomized, placebo-controlled, double-blind study in patients with mild-to-moderate OA.¹⁷ The patients in the placebo group underwent a mean joint space narrowing of 0.19 mm, compared to 0.04 mm of the GS group. This group also showed an improvement in the WOMAC and Lequesne's algo-functional indices. Another randomized, double blind, placebo-controlled trial, with a shorter follow-up than the above-mentioned two studies (6

months), showed no difference between GS (32% of responders) and placebo (33% of responders) in the assessment of pain in OA patients.¹⁸ The results of a comprehensive meta-analysis regarding randomized, placebo-controlled, clinical trials demonstrated the efficacy and safety of GS and CS in gonarthrosis.¹⁹ Indeed, evidence has been provided that a 3-month duration, twice a-year, intermittent treatment with CS can be useful in knee OA.²⁰ In this study, Lequesne's algo-functional index decreased by 36% and there was no evidence of joint space narrowing with a good tolerability.

Michel *et al.* conducted a two-year randomized, double-blind, placebo-controlled trial on patients with knee OA treated with C 4-6 Sulfate.²¹ Although there was no appreciable change in pain, stiffness or function, a joint space loss was observed in the placebo group whereas it was not evident in the CS group.

A 6-month, multicentre, double-blind, placebo- and celecoxib-controlled trial of 1583 patients showed that GS and CS alone or in combination – did not reduce pain.¹³ However, there was a statistically significant improvement in the subgroup of patients with moderate-to-severe pain. The adverse effects were mild and transient in all the groups.

Messier *et al.* compared a group of older adults with knee OA that underwent treatment with GS and CS combined with physical exercise, compared to a control group who received a placebo plus an exercise program.²² The main outcome measures were physical function, pain, and mobility. The GS and CS group was not superior to the placebo group.

A double-blind, placebo-controlled study (using acetaminophen as a side comparator) showed that patients who received GS achieved a greater improvement of the Lequesne's algo-functional index and WOMAC score compared to the patients of the placebo and acetaminophen groups.²³ Lequesne's algo-functional index decreased 3.1, 1.9 and 2.7 points respectively, and the WOMAC score showed an improvement of 39.6%, 33.3% and 21.2% respectively. The safety was good and comparable in the

three groups.

In a 2-year, placebo-controlled trial concerning joint space narrowing, there was no statistically significant difference between the placebo group and the GS and CS alone and in combination – groups.²⁴ The average joint space loss at two years was 0.16 mm. The blinded study protocol consisted of glucosamine hydrochloride (G) 500 mg 3 times daily, sodium chondroitin sulfate (CS) 400 mg 3 times daily, the combination of glucosamine and CS, placebo, or celecoxib 200 mg daily.

However, in patients with moderate OA Kellgren-Lawrence Grade 2 the results showed a trend of improvement relative to placebo.

In 2009 a review was made of meta-analyses and clinical trials concerning GS, GH and CS, alone and in combination.²⁵ The conclusion was that GS, GH and CS taken individually fail to show consistent efficacy in the treatment of OA, whereas GS and CS in combination are able to relieve pain in OA patients, with an excellent safety profile. On the contrary, a 2010 network meta-analysis, using pain intensity and joint space narrowing as main outcome measures, asserted that GS, CS and GS-CS in combination do not reduce pain in OA patients nor can have any impact on joint space narrowing.²⁶ Another meta-analysis recently performed by Miller *et al.* has confirmed that the effect of glucosamine and CS alone or in combination on OA is at best marginal.⁸ Nevertheless, these agents seem to have an acceptable safety profile, but the perceived benefit that some patients refer could represent a placebo response.

Gabay *et al.* present a randomised, double-blind, placebo-controlled clinical trial concerning the use of C 4S-6S for hand osteoarthritis.²⁷ In this trial they report a significant decrease of hand pain (difference in VAS=8.7 points) and a remarkable enhancement of hand function (improvement in Functional Index for Hand OA score of 2.14 points) in the CS group compared to the placebo group.

In the most recent meta-analysis of randomized, double-blind, placebo-controlled

trials, which included 3159 patients, it was shown that GH does not reduce pain in patients with OA, whereas GS may improve joint function in the same patients when administered for more than 6 months, however without pain relief.¹¹

Vitamin D

Vitamin D (VD) is a steroid hormone that plays a major role in calcium and phosphorus metabolism, which are essential for bone formation and mineralization. It is also involved in the maintenance of immune homeostasis,²⁸ and may influence chondrocytes in arthritic cartilage.²⁹ Indeed, Tetlow *et al.* observe that in arthritic cartilage there is a relationship between the VD receptor (VD-R) and MMP expression.³⁰ The activation of VD-R could enhance production of MMP-3 but could also suppress synthesis of MMP-9 and PGE2. However, the overall effect of VD on normal and arthritic cartilage is still unclear.

The relation of VD intake and serum levels with OA among participants in the Framingham Study shows that both low intake and low serum levels of vitamin D may lead to an increased risk of progression of knee OA.³¹

Uitterlinden *et al.* reported an association between VD-R genotype, VDR/COL2A1 locus, and OA.³² They suggest that VD-R polymorphisms may be involved in the production of osteophytes, and also that this association seems to be independent of joint space narrowing. This observation was not confirmed by successive studies. Lane observed that low serum levels of VD in elderly women may be associated with hip joint space narrowing, but without osteophyte growth.³³ Baldwin *et al.* examined the role of VDR/COL2A1 locus in hand or knee OA in the Framingham Osteoarthritis Study (FOS), and concluded that there is no relationship between VD-R polymorphisms and the development of OA.³⁴

A recent 3372-patient meta-analysis failed to find any association between OA development and other polymorphisms such as VD-R TaqI, BsmI and ApaI.³⁵

The results of two longitudinal cohort studies (the Framingham Osteoarthritis Study and the Boston Osteoarthritis of the Knee Study) failed to show any relationship between VD and the development of joint space narrowing in knee OA.³⁶ However, Ding *et al.* report that higher serum VD levels are associated with decreased joint space narrowing in knee OA in their study, which used Magnetic Resonance Imaging (MRI) on 880 randomly selected subjects.³⁷ These results were consistent in female patients with radiographic OA and knee pain, but not in men or in subjects without radiographic OA.

A consistent association between low serum VD levels and knee OA in younger patients (<60 years) has also been observed.³⁸ The mean VD in OA patients was significantly lower than controls (23.8 ng/mL *versus* 34.5 ng/mL). An even more notable association was observed in patients aged <55 years, whereas the association between OA and VD in older patients (≥60 years) was not significant.

Muraki *et al.* examined the association between FokI, Cdx2 and ApaI VD-R polymorphisms and serum VD level with knee pain and radiographic knee OA.³⁹ They report that VD level is not significantly associated with radiographic knee OA, whilst the lowest tertile of VD level may be associated with knee pain, but the evidence of this trial is weak.

A cross sectional study was performed on 99 patients to investigate the effect of VD on knee OA: 92 of the 99 patients (92.9%) had low VD serum levels, but the comparison of VD levels with radiological findings and functional classes showed no significant association.⁴⁰

A study has been carried out to verify if VD plays a role in the seasonal activity of rheumatoid arthritis, ankylosing spondylitis, and OA when compared to healthy controls.³⁰ Using the WOMAC score, the authors showed no relationship between VD serum levels and seasonal activity of knee OA.

A 2-year randomised, placebo-controlled, double-blind, clinical trial involved 146 pa-

tients with symptomatic knee OA.⁴¹ The aim of the trial was to establish whether VD supplementation, a dose sufficient to elevate VD plasma levels to higher than 36 ng/mL, may reduce the symptoms and progression of knee OA. Knee pain decreased in both groups, mean 2.31 in the treatment group and 1.46 in the placebo group, with no significant differences. The cartilage volume loss was the same – mean 4.30 and 4.25.

Laslett *et al.* present a 5-year longitudinal trial to investigate whether serum VD levels can predict change in knee and hip pain in older adults.⁴² They report that serum VD levels <25 nmol/L predicted change in knee pain over 5 years with a similar effect size for hip pain over 2.4 years and that correcting moderate vitamin deficiency may slow the worsening of knee or hip pain in the elderly.

Vitamin C

Vitamin C (VC), also called ascorbic acid, plays several roles in the biosynthesis of cartilage molecules. It is implicated in the synthesis of collagen fibrils, both dependently and independently through hydroxylation mechanisms, and of glycosaminoglycans, acting as a carrier of sulfate groups.²⁹ Vitamin C deficiency, thus, may impair not only the production of cartilage itself but also its quality. Furthermore, the well-known anti-oxidant properties of VC can exert a relevant chondroprotective role. There is evidence indeed, that oxidative stress may be a major player in the pathogenesis and development of OA.⁴³⁻⁴⁶

A Vitamin C supplement showed a slight chondroprotective effect in the development of spontaneous cartilage lesions in a guinea-pig model after partial medial meniscectomy.⁴⁷ On the other hand, Kraus *et al.* concluded that VC, at high dosage, activates latent TGF β .⁴⁸ Prolonged intra-articular exposure to TGF β has been shown to enhance the development of osteophytes in guinea pigs.

From the analysis of the Framingham Osteoarthritis Cohort, it was reported that a

high intake of VC may reduce the risk of disease progression in patients with OA, but also that it has no effect on the incidence of OA.⁴⁹

A cross-sectional trial on knee cartilage and bone in 293 healthy, middle-aged subjects (mean 58 years) shows that VC may reduce the size of bone osteophytosis and of subchondral bone marrow lesions, involved in the pathogenesis of knee OA.⁵⁰⁻⁵²

Nevertheless, a 2007 review of randomized clinical trials about the role of anti-oxidant (Vitamin A, C, E and Selenium) in the treatment of OA seemed to contradict the previous positive findings.⁵³ The clinical trials that assessed the efficacy of vitamin E in OA were considered methodologically weak and contradictory. The authors concluded that there was no convincing evidence that these anti-oxidants, alone or in combination, were effective in the treatment of OA.

In a recent longitudinal trial (the Clearwater Osteoarthritis Study), which looked at the effects of VC in the treatment of OA, patients underwent biennial, sequential knee radiographs, to determine the presence and progression of knee OA, comparing this to their self-reported VC intake.⁵⁴ The authors observed that subjects without knee OA who self-reported vitamin C supplement were 11% less likely to develop knee OA than subjects who self-reported no vitamin C supplement. Nevertheless, this trial failed to demonstrate any association between VC supplements and OA progression.

Boswellia serrata extracts

Boswellia serrata is a tree that grows predominantly in India. It produces a resinous gum that is widely used in Indian Ayurvedic medicine for its analgesic, anti-inflammatory, anti-arthritic and immuno-modulative properties.^{55, 56} The most common commercial preparations of *Boswellia serrata* extracts (BSE) are Aflapin® and 5-Loxin®. Over the last few years BSEs have attracted considerable attention for their use in the treatment of OA.

In a randomized, double-blind, placebo

controlled trial studying the use of BSE in 30 patients with knee OA (333 mg three times/day for eight weeks), a statistically significant decrease of knee pain and swelling, and an enhancement of flexion and walking distance was reported in the BSE group. Adverse events, most related to the gastrointestinal tract, were mild and transient.⁵⁷

Sengupta *et al.* reported a 90-day, double-blind, randomized, placebo-controlled trial of the efficacy and safety of 5-Loxin® (100 mg, and 250 mg/day) for knee OA treatment. Using Lequesne's Functional Index, and the WOMAC score, they concluded that the 250 mg/day dosage of 5-Loxin® significantly reduced the levels of the cartilage-degrading enzyme MMP-3 in synovial fluid, and decreased pain with an improved joint function. 5-Loxin® was shown to be safe, even in the long term.⁵⁸

In 2011 the same authors published a 90-day, double-blind, randomised, placebo-controlled study, to compare the efficacy and safety of 5-Loxin® and Aflapin® in the treatment of knee OA. They concluded that both 5-Loxin® and Aflapin® are able to relieve knee pain and improve physical function (Lequesne's Functional Index and WOMAC score). Better results were seen in the 100 mg Aflapin® group. Aflapin® was effective in inhibiting MMP-3 and ICAM-1 and thus, the inflammatory response. Safety parameters were almost the same in all the treatment groups and were mostly related to the gastrointestinal tract.⁵⁹

In a 30-day, double-blind, randomized, placebo-controlled clinical trial, Vishal *et al.* assessed the efficacy of Aflapin® in knee OA. They concluded that Aflapin® produced significant improvements in pain and function (Lequesne's Functional Index, and WOMAC score) as early as 5 days after the beginning of treatment, with a good safety profile.⁶⁰

Manganese

Manganese (Mn), like CS, is often marketed combined with other agents. It seems to be involved in the synthesis of GAGs and

proteoglycans and may also play an anti-oxidant role in the homeostasis of cartilage.

In a 31-patient randomized, double-blind, placebo-controlled trial, Leffler *et al.* observed that the combination of GS (1500 mg/day), CS (1200 mg/day) and Mn-ascorbate (228 mg/day) relieves symptoms of knee OA with a good safety profile.⁶¹ Also in an animal model, a combination of glucosamine, CS and Mn-ascorbate proved to be more efficacious than each single agent in inhibiting cartilage degradation.⁶² A combination of GH, CS and Mn-ascorbate was found to be effective compared to the placebo. Nevertheless, positive effects were observed only in patients with mild-to-moderate knee OA and not in patients with radiographically severe knee OA. The incidence of adverse events (in particular gastrointestinal dyspepsia) were similar in both groups.¹⁵

Mn-II-chloride was found to decrease the rate of the oxidative damage and therefore, HA degradation.⁶³ Likewise, in a mouse model, it was observed that the cationic complex MnTM-2-PyP(5+) which belongs to the superoxide dismutase class, prevents *in-vitro*-induced HA degradation.⁶⁴

Hyaluronic acid

Hyaluronic acid is a mucopolysaccharide comprised of tandem repeats of D-glucuronic acid and N-acetyl glucosamine that is abundantly present in the synovial fluid. At present, intra-articular administration of HA is one of the best treatments for patients with symptomatic knee OA, but it should be administered repeatedly.⁶⁵ In the light of these disadvantages, it is desirable to consider a less invasive administration of HA in the treatment of OA.

Twenty subjects aged ≥ 40 years with knee OA (Kellgren/Lawrence score ≥ 2) participated in a randomised, double-blind, controlled pilot trial. Ten subjects received a 80 mg/day dietary supplementation with a natural extract of chicken combs with a high content of hyaluronic acid (60%), and 10 subjects a placebo for 8 weeks. At 4 and 8 weeks, both groups showed statistically

significant improvements in WOMAC pain, stiffness, physical function subscales, and in the aggregate score, although the improvements were greater in the HA group.⁶⁶

In a randomised, double-blind, placebo-controlled study on 43 subjects with mild knee OA, Nagaoka *et al.* reported that daily administration of 60 mg of HA (from natural extract of chicken combs) increased collagen II (CII) synthesis and reduced CII degradation in the study group.⁶⁷ Response criteria, *i.e.*, “pain/walking function”, “pain/step-up and -down function” and “aggregate total symptoms” showed a greater improvement in the study group than in the placebo group. No diet-related side effects were observed.

Likewise, in 37 patients with severe knee pain (Kellgren/Lawrence score 2 or 3), who were aged 40 years or above, there was a significant improvement in WOMAC score after 4-weeks of oral intake of HA at the dosage of 200 mg/day, compared to the placebo group, with no adverse events.⁶⁸

In a randomised, double-blind, placebo-controlled trial, Tashiro *et al.* studied OA patients of 50 years or older (Kellgren-Lawrence grade 2 or grade 3); subjects took a 200mg/day dose of HA orally for 12 months, and performed quadriceps strengthening exercises and leg raising. They were evaluated at 2, 4, 6 and 12 months. Compared to placebo, the HA group showed an improvement in their knee symptoms, with decreased pain and stiffness, and subjects reported an enhanced health condition and ability to perform general activities.⁶⁹

Diacerhein

Diacerhein (and its active metabolite, rhein) is an Interleukin-1 (IL-1) inhibitor.⁷⁰ They have a moderate anti-inflammatory and analgesic effect. It has been shown to reduce IL-1-induced NO synthesis and to enhance COX-2 activity in chondrocytes.⁷¹ Diacerhein and rhein may also reduce the Interleukin-1-beta (IL-1 β)-induced MMP-13 production in OA sub-chondral bone.⁷²

Nguyen *et al.* report that diacerhein (like tenoxicam, with which it is compared) ap-

pears to be superior to placebo in the treatment of OA, although neither diacerhein nor tenoxicam appear to significantly enhance or detract from the efficacy of the other when they are administered concomitantly.⁷³

In a randomized, double-blind, placebo controlled trial, Pelletier *et al.* report that diacerhein, when used at a dose of 100 mg/day, was shown to be an effective treatment for symptoms in patients with knee OA, with VAS as primary measurement tool.⁷⁴

Concerning joint space narrowing, a three-year long therapy with diacerhein seems to have a significant structure-modifying effect, as compared with placebo, coupled with a good safety profile, in patients with hip OA.⁷⁵

A review of randomised controlled trials or quasi-randomised controlled trials, of placebo-controlled and comparative clinical trials, assumes that, even if more research is necessary to confirm the effectiveness and toxicity of diacerhein, there is evidence that it has a small, consistent benefit in pain reduction for patients with hip or knee OA.⁷⁰

Likewise, Rintelen *et al.* present a meta-analysis of 19 clinical trials, declaring that in the literature there is evidence for symptomatic efficacy of diacerhein in the treatment of knee and hip osteoarthritis, with a good safety profile.⁷⁶

It has also been reported that diacerhein, at a dosage of 100 mg/day, is as effective as sodium diclofenac at the dosage of 75 mg/day in the treatment of knee OA, and that it has a better extended effect with a good safety profile.⁷⁷

A randomised, double-blind, placebo-controlled trial (with percentage change from baseline in WOMAC score as measure), showed that diacerhein appears to be safe and effective for the treatment of knee OA and that it also has a long carry-over effect.⁷⁸

Comparing diacerhein and piroxicam, in a randomised, double-blind, NSAID-controlled study it was deduced that diacerhein is as effective as piroxicam in reducing pain and improving function but, unlike piroxicam, displays a carry-over effect and a better safety profile.⁷⁹

Brahmachari *et al.*, using a VAS and WOMAC score, report that diacerhein effectively reduces pain and improves physical function, with good tolerability, in early knee OA.⁸⁰

In a meta-analysis of randomized placebo-controlled trials, Bartels *et al.* report that diacerhein, although it has an increased risk of diarrhoea, is an alternative therapy for OA for patients who cannot take paracetamol or NSAIDs because of adverse effects or lack of benefit.⁸¹ However, the symptomatic benefit after 6 months remains unknown.

A double-blind, placebo-controlled trial shows that diacerhein, at the dosage of 50 mg twice/day, is ineffective in controlling the symptoms of hand OA. It is not reported any difference in pain and stiffness reduction and in function between the diacerhein and the placebo group.⁸²

Conclusions

Current scientific evidence gives little support for the use of DMOADs in clinical practice, and their effects on OA patients have so far been modest. Nevertheless it does suggest that they are feasibly an effective treatment if there is further development of existing and new drugs. Several agents have already proven DMOAD qualities and others offer potential properties *in vitro* that are yet to be tested in clinical trials. Further advances will be hastened by adopting new outcome measures such as MRI and biomarkers, and by the identification of groups of patients with similar features of disease.

Although the literature data show inconclusive evidence for the effectiveness of chondroprotective agents, the apparently good safety profile of these products has led patients, general practitioners and specialists to use them in the treatment of OA. According to the literature, the effectiveness of glucosamine and chondroitin sulphate, alone or in combination, in the treatment of OA seem to be marginal. Likewise, the studies that report the use of Vitamins C and D have shown conflicting results, and indeed

the research is of variable quality. With regard to the use of BSE, on the contrary, the literature seems to demonstrate noteworthy effectiveness and a good safety profile, although the research has been limited within Indian clinical practice. Mn can be useful to relieve the symptoms of OA, and it might be associated with other compounds in order to obtain a clinical benefit. Intra-articular administration of HA is one of the most common conservative treatments for patients with symptomatic knee OA, although oral HA therapy may also be a valid OA treatment, with none of the significant adverse events which accompany prolonged intra-articular HA use. Finally, the literature shows that diacerhein may be useful in the treatment of knee or hip OA. It also seems to have a good carryover effect and an acceptable safety profile.

Nevertheless, it is clear that further, scientifically rigorous, long-term, extended-size trials are needed to assess the role of these compounds in the treatment of OA. Several critical points remain to be addressed, but once these obstacles are overcome, this class of drug will represent a major achievement in the treatment of OA.

Riassunto

Nutraceutici e condroprotettori per il trattamento dell'osteoartrosi: una narrative review. Una risorsa controversa per il trattamento dell'osteoartrosi

Esistono numerosi integratori dietetici, agenti condroprotettori, farmaci modificanti il decorso di una malattia e prodotti naturali che sono stati sviluppati e prodotti per trattare pazienti affetti da osteoartrosi (OA). Essi possono essere, e spesso sono, messi in commercio senza essere sottoposti ad un'accurata valutazione scientifica. In letteratura è possibile reperire numerosi trial *in vivo* o *in vitro* riguardanti questi prodotti, ma vi è mancanza di studi di alta qualità, a lungo termine, prospettici e comparativi in grado di dimostrare con certezza la loro efficacia nel trattamento dell'osteoartrosi. La seguente è una narrative review riguardante i più comuni agenti condroprotettori presenti sul mercato che ha come obiettivo lo stabilire, sulle basi della più recente letteratura, se questi prodotti possano avere un ruolo nel trattamento dell'osteoartrosi.

PAROLE CHIAVE: Osteoartrosi - Cartilagine - Glucosamine - Vitamina D - Vitamina C.

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