New Perspectives in the Management of Osteoarthritis. Structure Modification: Facts or Fantasy?

JEAN-YVES REGINSTER, OLIVIER BRUYERE, and YVES HENROTIN

ABSTRACT. Several entities have been carefully investigated for the symptomatic and structural management of osteoarthritis (OA). The most compelling evidence of a potential for inhibiting the structural progression of OA has been obtained with glucosamine sulfate, while some preliminary results also suggest that other compounds could be used in the same indication. At any rate, several medications have clearly demonstrated a symptomatic action, mainly in OA of the lower limbs, including pain relief and improvement of functional disability. An important issue is that all conclusive studies with such chemical entities resulted from the use of prescription medicines and not over-the-counter or nutriceutical supplements. (J Rheumatol 2003;30 Suppl 67:14–20)

Key Indexing Terms:
OSTEOARTHRITIS STRUCTURE MODIFICATION STRONTIUM RANELATE
GLUCOSAMINE SULFATE CHONDROITIN SULFATE DIACEREIN TREATMENT

INTRODUCTION

Due to the rapidly aging population today, osteoarthritis (OA) is now considered a major public health issue in most developed countries. Up to 10% of the world population suffers from OA, and it has been estimated that more than 50% of those aged over 50 years are affected[1].

For decades, the traditional pharmacological management of OA has been mainly symptomatic without well documented influence on the duration of the disease and its progression. However, in recent years, several sets of guidelines, recommendations, or points to consider have been issued by regulatory authorities[2,3] or scientific groups[4] regarding requirements for registration of drugs to be used in the treatment of OA. The ideal outcomes currently include pain and function assessment for symptom-modifying drugs, and joint space narrowing assessed by plain radiography for structure-modifying compounds. Taking advantage of these more precise recommendations, several chemical entities have been carefully investigated for the management of OA. While some of them are available as over-the-counter (OTC) or nutriceutical supplements in several countries, most of the investigations performed with these molecules have not been undertaken with such products but with molecules registered and marketed as prescription drugs and having fulfilled all the requirements for quality and safety at the level of the health authorities. We will summarize the available evidence that some compounds can effectively interfere with either the symptoms of OA or structural progression of the disease.

From the Bone and Cartilage Metabolism Research Unit, University of Liège, and the WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases, Liège, Belgium.

J.Y. Reginster, MD, PhD, Professor of Epidemiology and Public Health, University of Liège, Director, WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases; O. Bruyere, MD, Assistant, Department of Epidemiology and Public Health, University of Liège, WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases; Y. Henrotin, MD, Department of Epidemiology and Public Health, University of Liège.

Address reprint requests to Dr. J-Y. Reginster, Bone and Cartilage Metabolism Research Unit, CHU Centre-Ville, Policliniques L. Brull, Quai Godefroid Kurth 45 (9ème étage), 4020 Liege, Belgium. E-mail: jyreginster@ulg.ac.be

Chondroitin Sulfate

Chondroitin sulfate (CS) is a major component of the extracellular matrix from many connective tissues, including but not limited to cartilage, bone, skin, ligaments, and tendons. CS is a sulfated glycosaminoglycan, composed of a long unbranched polysaccharide chain with a repeating disaccharide structure of N-acetylgalactosamine and glucuronic acid[5,6]. Most of the N-acetylgalactosamine residues are sulfated, particularly in the 4- or 6-position, making CS a strongly charged polyanion with high water-draining power. In the articular cartilage, the high content of CS in the aggrecan plays a major role in creating considerable osmotic swelling pressure that expands the matrix and places the collagen network under tension[5].

In OA, changes in the structure of CS were reported in different models, with the apparition of a longer chain length and the chains containing more epitopes recognized by specific antibodies[5,7]. In a model of human articular chondrocytes, cultivated in clusters, CS (100–1000 µg/ml) increased the production of proteoglycans, with no detectable effects on collagen II synthesis. In the presence of interleukin 1ß (IL-1ß), CS counteracted the effects of the cytokines on the proteoglycans collagen II and prostaglandin E_2 (PGE_2 synthesis), suggesting that in this particular model CS can reduce collagenolytic activity and increase matrix component production[8]. In articular chondrocytes isolated from rabbits, CS (100 µg/ml) decreased

(average 28%) the number of apoptotic cells, after exposure to nitric oxide donors (sodium nitroprussite)[9].

In rabbits injected with chymopapain into the knee joint, oral administration of CS, and to a lesser extent intramuscular injections of CS, started 10 days prior to chymopapain injection, prevented, 84 days after chymopapain, the reduction in cartilage proteoglycan content, suggesting that CS may have a protective effect on the damaged cartilage, allowing it to continue to resynthesize proteoglycans[10].

Several clinical trials have investigated the effects of CS administration in patients with OA. In 127 patients with uni- or bilateral knee OA (Kellgren-Lawrence radiographic scores grade I to III), 1200 mg/day of CS, given either as a single daily oral dose or as 3 × 400 mg, improved spontaneous joint pain [visual analog scale (VAS) 50%], and Lequesne index (40–45%) over 3 months, compared to placebo (10–15%)[11]. In a similar population (n = 146), the same dose of CS (3 × 400 mg/day) was compared to the daily intake of 3 × 50 mg of diclofenac sodium. Lequesne index, spontaneous pain, and pain on loading were promptly (day 30) and drastically (35–50% at day 30 and 40–50% at day 90) reduced with nonsteroidal antiinflammatory drugs (NSAID); however, these reappeared at the end of the 3-month treatment. With CS, the therapeutic response appeared later (day 60), was of higher magnitude at the end of the 3-month treatment (80–85%), and lasted for up to 3 months after the end of the treatment (50–80% at day 180)[12]. In a dose-ranging study comparing CS at 200 mg, 800 mg, and 1200 mg daily to placebo in 140 patients with knee OA over a 3-month period, the lowest dose was not found more effective than placebo. The 2 higher doses showed a similar profile of efficacy, significantly different from 200 mg/day and from the placebo on pain (VAS) and Lequesne index[13].

The dose of 800 mg/day of CS was further tested in 2 other double-blind, placebo controlled trials, including 85 and 140 patients[14,15] and focusing on knee OA, with results within the same order of magnitude. Interestingly, one of the trials[14] also showed significant improvement in the CS group (10% vs 0% change in the placebo group) in the walking time, defined as the minimum time to perform a 20-meter walk. In the other study[15], quantitative analysis of joint space carried out after 12 months using a digitized automatic image analyzer showed a decrease in the placebo group of the surface area, minimum width, and mean thickness of the medial femorotibial joint, whereas no change could be observed in the CS treated group[15].

The structure-modifying properties of CS were also assessed in a double-blind placebo controlled trial including 119 patients with interphalangeal OA. After 3 years, the group taking 3 × 400 mg/day of CS had a significant decrease in the number of patients with new "erosive" OA finger joints (8.8%) compared to the placebo group (29.4%).

In a recent communication, Michel, *et al* reported the preliminary results of a 2-year prospective, double-blind study comparing the changes in femorotibial joint space observed in 300 patients randomized to either 800 mg/day CS or placebo. In 151 subjects (out of a total of 210 completers) who had a minimum joint space width ≥ 1 mm at entry, the authors reported a significant effect of CS versus placebo on the evolution of minimum joint space width ($p < 0.03$) or mean joint space thickness ($p < 0.01$) but not surface area (NS). Detailed numerical results should be provided in the near future[16].

Glucosamine Sulfate

Glucosamine is an aminosaccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans and cartilage[17]. Due to the essential role played by aggrecans in giving the cartilage its hydrophilicity, compounds enhancing their synthesis might be beneficial in OA, a disorder characterized by an increase in matrix structural protein turnover, with catabolism being predominant over synthesis.

In human osteoarthritic chondrocytes, glucosamine sulfate (GS) was tested for its ability to regulate the expression of genes, encoding constitutive extracellular matrix macromolecules. GS (50 µM) induced a 2-fold increase in the steady levels of both perlecan and aggrecan mRNA and caused a modest but consistent decrease in the levels of stromelysine mRNA[18]. The same authors later reported that GS not only increased the expression of the aggrecan core protein but also downregulated, in a dose-dependent manner, both matrix metalloproteinases I and III expression[19]. These studies suggested that GS may exert beneficial effects in OA due to its effects on the balance between synthesis and degradation of extracellular cartilage and on articular cartilage function.

These transcriptional effects were supported by reports that when using a model of human chondrocytes from osteoarthritic femoral heads cultivated in a 3-dimensional system for 12 days, GS (10–100 µg/ml) increased proteoglycan synthesis with no effect on their physicochemical form, on type II collagen production, or on cell proliferation, as assessed by quantifying DNA synthesis[20].

Glucosamine also inhibited, in a rat chondrosarcoma cell line and bovine cartilage explants, aggrecan degradation, which was mediated by aggrecanase, a proteinase induced by IL-1 or retinoic acid[21]. The inhibition of aggrecanase response was reported to be a consequence of metabolic changes that followed a marked increase in the intracellular glucosamine concentration, the exact mechanisms thereof being not yet fully elucidated. More recently, N-acetylglucosamine was shown to suppress IL-1ß and tumor necrosis factor-α induced nitric oxide production in human articular chondrocytes, together with an inhibition of inducible nitric oxide synthase mRNA and protein expression. In the same experiment, N-acetylglucosamine also suppressed produc-

tion of IL-1ß induced cyclooxygenase II and IL-6, with no effect on the constitutively expressed cyclooxygenase I[22]. These results support, while identifying novel mechanisms, the antiinflammatory properties of GS, which were described in various classical models, including the carrageenan-induced pleuritides or inflamed paw in the rat[17].

On the other hand, osteoarthritic cartilage is also characterized by a potential defective repair process, related to the inability of proliferated cells to migrate in damaged areas. Osteoarthritic fibrilated cartilage was associated with a highly significant decrease in chondrocyte adhesion to extracellular matrix proteins and, more specifically, to fibronectin[23]. In chondrocytes isolated from fibrilated areas of cartilage from osteoarthritic femoral heads, GS (50–500 µM) restored their decreased adhesion to fibronectin[24]. The authors suggested that activation of protein kinase C, considered to be involved in the physiological phosphorylation of the α-6 A integrin subunit, could be one of the possible mechanisms through which GS restores fibrilated cartilage chondrocyte adhesion to fibronectin, hence improving the repair process in osteoarthritic cartilage[24].

In rabbits with transection of the anterior cruciate ligament, GS (120 mg/kg/day) significantly reduced (after 8 weeks) the level of chondropathy measured by both an 8-grade macroscopic score and an overall assessment using a 100 mm VAS[25].

Efficacy and safety of GS were tested in several randomized, controlled, clinical trials, in patients with OA, predominantly OA of the knee or spine. In knee OA, intramuscular GS (400 mg twice a week for 6 weeks) was compared to a placebo (n = 155). A significant difference in the decrease in Lequesne index was observed for the GS group versus placebo, both at the end of treatment and 2 weeks after drug discontinuation. The response rate (i.e., at least a 3-point reduction in Lequesne index) was significantly higher in the GS group when considering evaluable patients (55% vs 33%) or by intention-to-treat analysis (51% vs 30%)[26]. In humans, pharmacokinetic studies have shown that, after oral administration of GS, almost 90% was absorbed. When using ^{14}C labelled GS, the radioactivity incorporated in the plasma proteins follows similar pharmacokinetic patterns after oral, intravenous, or intramuscular administration. However, the area under the curve obtained after oral administration is 26% of that after intravenous or intramuscular administration[27]. Therefore, in order to optimize longterm compliance of osteoarthritic patients, the oral form of glucosamine was predominantly used in subsequent clinical trials. In 252 outpatients with OA of the knee (stage I, III), subjects treated with 1500 mg/day GS for 4 weeks had a decrease in Lequesne index significantly higher than those receiving a placebo. The response rates (same criteria as in Reference 10) were within the same range as observed with the intramuscular formulation (55% vs 38% in evaluable patients and 52% vs 37% patients in intention-to-treat analysis)[28].

In a 3-year trial, including 319 patients randomized to either 1500 mg/day of GS or placebo, preliminary results suggested that GS significantly improved the longterm symptomatic evolution of knee OA assessed by Lequesne algofunctional index[29]. Noteworthy is the observation that glucosamine hydrochloride does not induce symptomatic relief in knee OA to the same extent as GS does. In an 8-week double-blind, placebo controlled study, followed by 8 weeks of off-treatment observation, glucosamine hydrochloride yielded beneficial results only in response to a daily diary pain questionnaire, with no effects on the primary endpoint (WOMAC questionnaire)[30]. This obviously raises the question, so far unanswered, of the importance of sulfate and of its contribution to the overall effects of glucosamine.

GS (1500 mg/day) was also compared to placebo in 160 outpatients with spinal OA (68 with cervical, 57 with lumbar, and 37 with both spinal sites) and induced a significant improvement of pain and function variables (VAS) at both sites. The improvement in glucosamine therapy lasted up to 4 weeks after drug discontinuation[31]. The symptomatic action of GS was also compared to that of NSAID: GS 1500 mg per os and ibuprofen (Ibu) 1200 mg, daily, resulted in the same success rate (GS 48% vs Ibu 52%) after 4 weeks in 200 hospitalized patients with knee OA, notwithstanding the effect of Ibu, which tended to be sooner than with GS (48% Ibu vs 28% GS after first week of treatment). However, significantly fewer patients reported adverse events (mainly of gastrointestinal origin) with GS (6%) than with Ibu (35%), and the number of adverse event related dropouts was different between the 2 groups (7% Ibu vs 1% GS)[32]. These results were duplicated in a sister study, performed in 68 Chinese patients, with a nonsignificant difference between Ibu and GS (trend in favor of GS) in the reduction of the symptoms of OA, but GS being significantly better tolerated (6% of patients with adverse reactions and 0% of drug related dropouts) than Ibu (16% of adverse reactions and 0% of drug related dropouts)[33]. Three hundred nineteen patients with symptomatic OA of the knee received either GS (1500 mg/day), piroxicam (20 mg/day), both drugs, or placebo for 12 weeks followed by 8 weeks without treatment. In the GS group, the Lequesne index decreased by 4.8 points during treatment, for a decrease of 2.9 and 0.7 points, in the piroxicam and placebo groups, respectively ($p < 0.001$). The association did not differ from GS alone. GS did not differ in safety (14.8% incidence of adverse events during treatment) from placebo (23.7%), but was significantly better tolerated than piroxicam (40.9%) or the association (35%). The improvement in GS treated patients persisted during the 8-week followup period, whereas the improvement with piroxicam did not[34].

To test the longterm effects of GS on the progression of

OA knee joint structural changes and symptoms, 212 patients with knee OA [by American College of Rheumatology (ACR) criteria] were randomly assigned in a double-blind fashion to continuous treatment with GS (1500 mg once daily) or placebo for 3 years[35]. Weight-bearing, anteroposterior radiographs of each knee were taken at enrolment and after 1 and 3 years, standardizing patients' positioning and radiographic procedures. Total mean joint space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis based on a validated computerized algorithm, with the narrowest joint space at enrolment being taken for the primary evaluation (signal joint). Symptoms were scored at each 4-month visit by a total WOMAC index. Placebo treated patients had an average joint space narrowing of –0.31 [–0.48 to –0.13 mm], while no joint space narrowing [–0.06 (–0.22 to 0.09 mm)] occurred in the group treated with GS ($p = 0.043$). Further, the percentage of patients who experienced a clinically relevant (> 0.5 mm) mean joint space narrowing after 3 years was significantly ($p = 0.013$) lower in the GS group (15%) than in the placebo group (30%).

This study was later confirmed by a similar trial in a population of 202 subjects from both sexes with a slightly worse degree of knee OA. In this trial, the sparing effect of 1500 mg/day GS on the rate of progression of the disease was statistically significant as early as the first year and remained so until the end of the 3-year followup. The authors also described a significant ($p = 0.03$) reduction in the proportion of patients worsening their osteophyte score at the endpoint (20% in the placebo vs 6% in the GS group)[36].

A slight worsening in symptoms was evident at the end of treatment with placebo, compared to the improvement observed after GS[36].

The safety profile of GS was evaluated in a systematic review of 12 randomized controlled trials and was deemed excellent, with 7 patients out of 1486 randomized to GS withdrawn for GS related toxicity and only 48 having reported any GS related adverse reactions[37].

Further, an open study carried out by 252 doctors throughout Portugal evaluated the tolerability of GS in 1208 patients. Patients were given GS 500 mg orally 3 times a day, for a mean period of 50.3 days (range 13 to 99 days). Eighty-eight percent of the patients reported no side effects. In the remaining 12% of the study population, the reported adverse effects were generally mild in severity and predominantly affected the gastrointestinal tract (e.g., epigastric pain, heartburn, and diarrhea). All reported complaints were reversible with discontinuation of GS[38]. While some questions were raised regarding the role of glucosamine in glucose metabolism[39] and the possibility of increased insulin resistance, a detailed review of scientific studies performed with GS ruled out this possibility and reemphasized the safety of short and longterm use[40].

Avocado/soybean Unsaponifiables

The unsaponifiable part of avocado (A) and soybean (S) oils (ASU) mixed in a ratio of 1:2 (A1S2) has been investigated in the treatment of connective tissues including OA for several years[41-43]. ASU was reported to significantly increase collagen synthesis by articular chondrocytes isolated from rabbits, without interfering with the balance between the different types of collagen[44]. In the same experiment, ASU partially reversed the inhibitory effect of IL-1 on collagen synthesis[44]. In a model of rabbit articular chondrocytes and human rheumatoid synovial cells, the same authors demonstrated that ASU partially reversed the IL-1 mediated collagenolytic effect in synovial cells and totally blocked it in chondrocytes[45]. More recently, we confirmed, in a short term culture of human chondrocytes, that ASU (3.3 to 10 µg/ml) reduced spontaneous production of stromelysin, IL-6, IL-8, and PGE_2 by chondrocytes. Inhibition of IL-6 production was more specifically performed by avocado residues, but ASU mixtures had a more pronounced inhibitory effect on cytokine production than avocado or soybean residues alone. ASU also partially reversed the IL-1ß induced release of collagenase, stromelysin, IL-6, IL-8, and PGE_2 by human chondrocytes[46]. In bovine articular chondrocytes, ASU stimulated expression of transforming growth factor-ß1 (TGF-ß1), TGF-ß2, and plasminogen activator inhibitor 1[47]. All these elements suggest that ASU induces stimulation of matrix synthesis, TGF-ß expression in chondrocytes, and by blocking metalloproteinase activation and cytokine release also prevents cartilage degradation and promotes matrix repair mechanisms in articular cartilage.

In a 3-month prospective, randomized, double-blind placebo controlled trial, ASU given for 45 days reduced the need for NSAID treatment in 164 patients with hip or knee OA. The time spent off NSAID therapy beyond day 54 was also shorter in the placebo group[48]. However, the main demonstration of the symptomatic effect of ASU in knee and hip OA came from a 6-month randomized, double-blind placebo controlled trial[46], where patients with primary OA of the knee ($n = 114$) or hip ($n = 50$) received ASU 300 mg daily or placebo for 6 months, followed by a 2-month post-treatment followup. The mean Lequesne functional index decreased from 9.7 to 6.8 in the ASU group and from 9.4 to 8.9 in the placebo group ($p < 0.001$) at the end of the 6-month treatment period. Pain also decreased significantly more ($p < 0.003$) and NSAID intake was slightly lower in the ASU group. A residual effect was still observed at month 8. These results suggest that ASU has significant symptomatic efficacy in the treatment of OA from the second month of administration, and shows a persistent effect after the end of treatment. A pilot randomized, double-blind placebo controlled trial failed to demonstrate a structural effect of ASU in 163 patients with painful hip OA followed for 2 years. However, in a post-hoc analysis, ASU signifi-

cantly reduced the progression of joint space loss (–0.43 ± 0.51 mm) compared to the placebo group (–0.86 ± 0.22 mm) in a subgroup of patients with the most affected joints at baseline (joint space width below the median, i.e., 2.45 mm). Clinical variables in the 2 groups did not differ significantly throughout the study[49].

Diacerein

Diacerein, a purified compound with anthraquinonic structure, has been shown to inhibit *in vitro* and *in vivo* the production and activity of IL-1 and the secretion of metalloproteases, without affecting prostaglandin synthesis. In several animal models, diacerein has shown beneficial effects on cartilage by preventing or reducing the macroscopic and microscopic lesions of the joint tissue. Further, in several clinical trials of 2–6 months' duration, diacerein significantly reduced pain and functional impairment in patients with hip or knee OA compared with placebo[50].

In a randomized, double-blind, placebo controlled 3-year study, 507 patients with primary OA of the hip (by ACR criteria) received diacerein (50 mg twice a day) or placebo. The minimal hip joint space width was measured by a central reader on yearly pelvic radiographs, using a 0.1 mm graduated magnifying glass[50].

Baseline characteristics were comparable in the 2 treatment groups (255 patients receiving diacerein, 252 receiving placebo); 238 patients (47%) discontinued the study, mainly because of adverse events in the diacerein group (25% vs 12% with placebo) and because of inefficacy in the placebo group (14% vs 7% with diacerein). The percentage of patients with radiographic progression, defined by a joint space loss of at least 0.5 mm, was significantly lower in patients receiving diacerein than in patients receiving placebo, both in the intent-to-treat analysis and in the completer analysis [50.7% vs 60.4% (p = 0.036) and 47.3% vs 62.3% (p = 0.007), respectively]. In the intention-to-treat analysis, the annual difference in joint space width observed in patients having received the placebo (0.39 ± 0.81 mm) did not differ significantly from the one observed in patients treated with diacerein (0.39 ± 0.75 mm). In patients who completed 3 years of treatment, the rate of joint space narrowing was significantly lower with diacerein (mean ± SD 0.18 ± 0.25 mm/year vs 0.23 ± 0.23 mm/year with placebo; p = 0.042). Diacerein had no evident effect on the symptoms of OA in this study. However, a post-hoc covariate analysis that took into account the use of analgesics and antiinflammatory drugs showed an effect of diacerein on Lequesne functional index. Diacerein was well tolerated during the 3-year study. The most frequent adverse events were transient changes in bowel habits.

Miscellaneous

Ginger. Ginger extracts have been suggested to interfere with the physiological process of rheumatic disorders[51,52]. While their mechanism of action remains largely unknown, interaction with tumor necrosis factor-α (TNF-α) expression in synoviocytes was suggested (C. Frondoza, personal communication). In a double-blind, double-dummy, crossover study performed in 40 patients with OA of knee or hip, an extract of selected Chinese ginger (EV.EXT.33) was ranked between Ibu and placebo in terms of pain relief and improvement of function[53]. In a preliminary report, a highly concentrated and standardized extract (EV.EXT.77) of 2 ginger species, *Zingiber officinale* and *Alpinia galanga* (3 g and 1.5 g per tablet, respectively) was tested for 6 weeks versus placebo in 261 patients with OA of the knee. EV.EXT.77 had a moderate but clinically relevant and statistically significant effect on symptoms of OA, mainly on knee pain on standing (p = 0.048), but gastrointestinal adverse events were more frequent in the ginger extract than in the placebo group (49 vs 11 patients). Longterm efficacy and safety of ginger extracts should be fully evaluated in more extensive clinical trials[54].

Strontium ranelate. Based on previous studies showing that strontium ranelate modulates bone loss in osteoporosis, it could be hypothesized that this drug also is effective on cartilage degradation in OA. This was investigated *in vitro* on normal and OA human chondrocytes treated or not treated with IL-1ß. Strontium ranelate strongly stimulated PG production. Moreover, 10^{-3} M strontium ranelate increased the stimulatory effect of IGF-I (10^{-9} M) on PG synthesis, but did not reverse the inhibitory effect of IL-1ß.

Strontium ranelate strongly stimulates human cartilage matrix formation *in vitro* by a direct ionic effect without stimulating the chondroresorption processes. This finding provides a preclinical basis for *in vivo* testing of strontium ranelate in OA[55].

Intraarticular hyaluronic acid. In a pilot open clinical trial on 40 patients with knee OA, the structural changes in the synovial membrane and cartilage following treatment with intraarticular hyaluronic acid given as 5 weekly injections (20 mg/2 ml once a week for 5 weeks) were evaluated by microarthroscopy and morphological analysis of biopsy samples taken at baseline and after 6 months, under blind conditions.

At 6 months, the microarthroscopic evaluation indicated that the majority of the patients (60%) showed no changes compared to baseline, while 32.5% of the patients showed improvement in the grading and/or extension of cartilage lesions and 7.5% showed a worsened condition. These changes were accompanied by a statistically significant reduction in the synovial inflammation (p = 0.001).

Results were confirmed by morphological examination of the cartilage and synovial membrane.

At 6 months compared to baseline, a statistically significant reconstitution of the superfical amorphous layer of the cartilage (p = 0.0039), improvement in chondrocyte density (p = 0.0023) and vitality (p = 0.05), and a statistically signif-

icant reduction in synovial inflammation (p = 0.0001) accompanied by a significant increase in the synovial repair process (p = 0.0001) were observed[56].

CONCLUSION

Several compounds have shown symptomatic and/or structural efficacy in OA. So far, the most compelling evidence of a potential for inhibiting the progression of OA is obtained with glucosamine sulfate, while some hints also suggest that chondroitin sulfate, diacerein, or avocado/soybean unsaponifiables could be used in the same indication. These compounds, however, have clearly demonstrated a symptomatic action, mainly in OA of the lower limbs. Other compounds, including ginger extracts, strontium ranelate, and hyaluronic acid, should be investigated more extensively. All conclusive results were obtained with prescription drugs containing these substances and should not be extrapolated to OTC or food supplements whose content, pharmacokinetics, and pharmacodynamics are not guaranteed.

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