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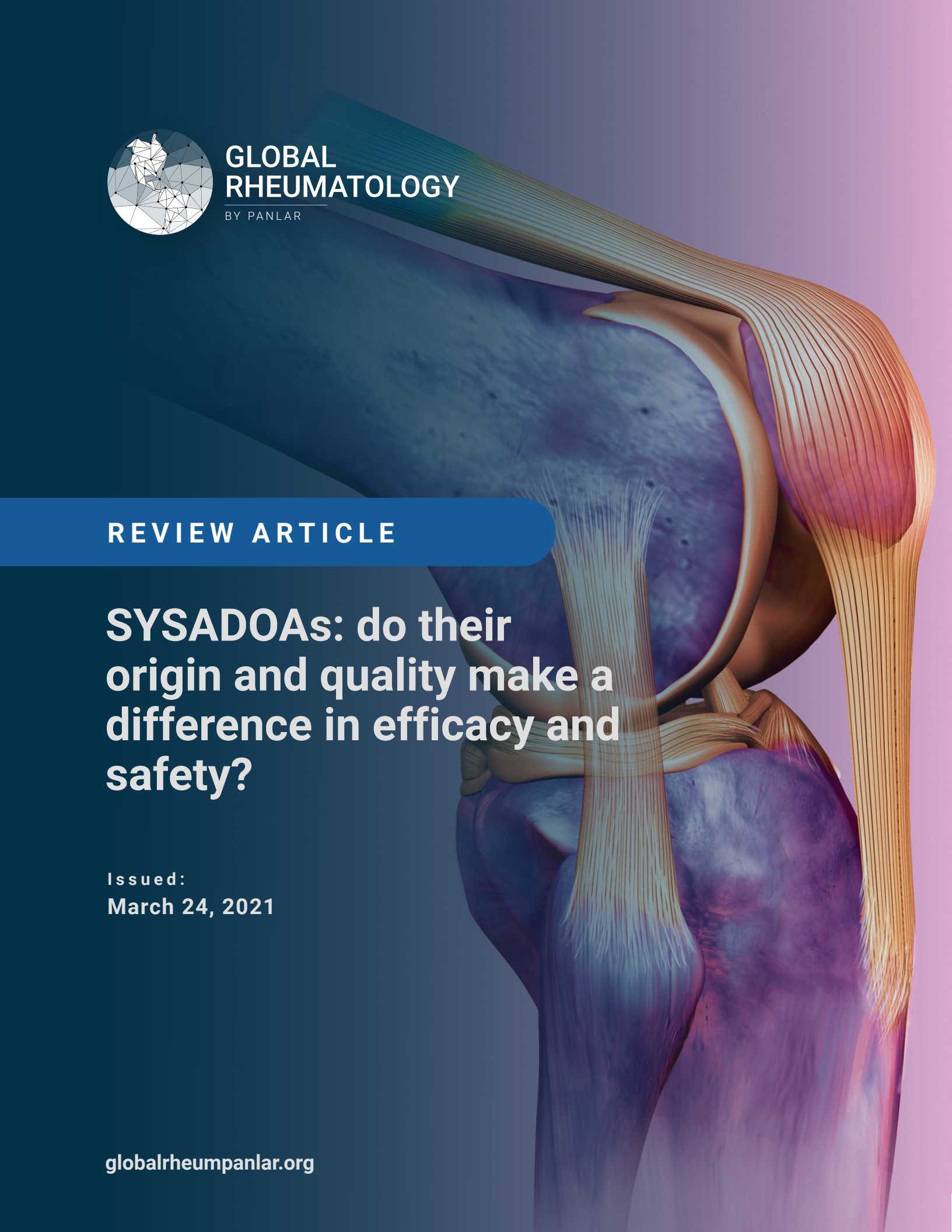

REVIEW ARTICLE

SYSADOAs: do their origin and quality make a difference in efficacy and safety?

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SYSADOAs: do their origin and quality make a difference in efficacy and safety?

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Summary

In English

Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) comprise a heterogeneous group of drugs with a long-term effect on the symptoms of osteoarthritis. The most widely used agents—chondroitin sulfate, glucosamine, and diacerein—have been recommended by the European League Against Rheumatism (EULAR) and by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). However, prescription of SYSADOAs is challenging owing to the large number of agents available and the fact that variations in extraction and purification techniques can lead to differences in content, composition, purity, biological effects, and safety. Moreover, differences in the regulation of pharmaceutical-grade products and nutraceutical-grade products lead to variations in quality and content between the two classes of products. Despite criticisms that their symptom-modifying effects are mild or insignificant, SYSADOAs have been shown to reduce pain and stiffness and increase functional capacity while exerting a chondroprotective effect in patients with knee and hand osteoarthritis. Recent international guidelines have proposed that chondroitin and glucosamine be the treatment of choice in osteoarthritis, especially in patients with comorbidities taking multiple medications, owing to their safety profile. Safety and efficacy should therefore be evaluated when prescribing SYSADOAs taking into account these differences, and health care providers should make every effort to make patients aware of the existing differences between products. This review discusses the use of SYSADOAs in the treatment of osteoarthritis, with emphasis on safety and effectiveness and how these are affected by the quality and origin of the agents.

Summary
In Spanish

Los medicamentos sintomáticos de acción lenta para la artrosis (SYSADOA) comprenden un grupo heterogéneo de medicamentos con efecto a largo plazo sobre los síntomas de la artrosis. Los más utilizados (condroitina sulfato, glucosamina y diacereína) han sido recomendados por el EULAR y por el ESCEO. Sin embargo, la prescripción de SYSADOA es controvertida debido a la gran cantidad de productos disponibles y a que las variaciones en las técnicas de extracción y purificación pueden dar lugar a diferencias en el contenido, la composición, la pureza, los efectos biológicos, la seguridad. Las diferencias en la regulación de productos de grado farmacéutico y nutracéutico provocan variaciones en calidad y contenido.

Aunque las críticas de que sus efectos modificadores de los síntomas son leves o insignificantes, está demostrado que los SYSADOA reducen dolor y rigidez aumentando la capacidad funcional mientras ejercen un efecto condroprotector en pacientes con artrosis de rodilla y mano. Guías internacionales han propuesto que la condroitina y la glucosamina sean el tratamiento de elección en la artrosis, especialmente en pacientes con comorbilidades que toman múltiples medicamentos. La seguridad y la eficacia deben evaluarse teniendo en cuenta estas diferencias, y los proveedores de atención médica deben hacer todo lo posible para que los pacientes sean conscientes de las diferencias existentes entre los productos. Esta revisión analiza el uso de SYSADOA en el tratamiento de la artrosis, con énfasis en la seguridad y eficacia y cómo estas se ven afectadas por la calidad y el origen de la materia prima.

Summary
In Portuguese

Os medicamentos sintomáticos de ação lenta para a osteoartrite (SYSADOAs) constituem um grupo heterogêneo de medicamentos com efeito de longo prazo nos sintomas da osteoartrite. Os agentes mais amplamente usados - sulfato de condroitina, glucosamina e diacereína - foram recomendados pela EULAR e pela ESCEO. Entretanto, a prescrição de SYSADOAs é desafiadora devido ao grande número de agentes disponíveis e ao fato de que variações nas técnicas de extração e purificação podem levar a diferenças no conteúdo, composição, pureza, efeitos biológicos e segurança. As diferenças na regulamentação de produtos de grau farmacêutico e produtos de grau nutracêutico levam a variações na qualidade e no conteúdo entre as duas classes de produtos. Apesar das críticas de que seus efeitos modificadores dos sintomas são leves ou insignificantes, os SYSADOAs demonstraram reduzir a dor e a rigidez e aumentar a capacidade funcional enquanto exercem um efeito condroprotetor em pacientes com osteoartrite de joelho e mão. Diretrizes internacionais recentes propuseram que a condroitina e a glucosamina sejam o tratamento de escolha na osteoartrite, especialmente em pacientes com comorbidades em uso de vários medicamentos, devido ao seu perfil de segurança. A segurança e eficácia devem, portanto, ser avaliadas ao prescrever SYSADOAs levando em consideração essas diferenças, e os profissionais de saúde devem fazer todos os esforços para alertar os pacientes sobre as diferenças existentes entre os produtos. Esta revisão discute o uso de SYSADOAs no tratamento da osteoartrite, com ênfase na segurança e eficácia e como estes são afetados pela qualidade e origem dos agentes.

Introduction

Osteoarthritis, the most common form of arthritis, is a frequent, progressive, degenerative joint disease that leads to functional limitation and diminished quality of life [1]. It is characterized by loss of cartilage and synovial fluid, bone degradation, and inflammation and is a leading cause of chronic pain [2]. The complex and heterogeneous nature of the pathophysiology of osteoarthritis involves a dynamic interaction between biological, biomechanical, and genetic components [2, 3]. Overuse of joints and altered joint mechanics can result in destruction of chondrocytes and disruption of the extracellular matrix, and, eventually, detrimental changes in cartilage function that lead to osteoarthritis [3]. Activation of chondrocytes in response to chemical and mechanical stimuli results in the production of pro-inflammatory cytokines that play an important role in the pathogenesis of osteoarthritis [2].

Today, osteoarthritis has been reported to affect about 300 million people worldwide, and its prevalence is increasing owing to the aging of the population and obesity [4, 5]. As a disabling condition, osteoarthritis impacts daily living. It is associated with different grades of disability, ranging from mild, intermittent pain with only minimal difficulty performing daily activities to severe chronic pain, progressive structural damage, and loss of function, all of which are often associated with a decline in mental health, as well as an increase in mortality when a person is no longer able to walk or live independently. Osteoarthritis generates considerable disability, and the cost of the disease could reach 0.25%-0.50% of gross domestic product. The real burden of the disease may have been underestimated, and it could prove very difficult to calculate the indirect costs of the disease in terms of social support, lost productivity, and wage losses [6].

The different phenotypes and degrees of severity and the chronic nature of the disease mean that various therapeutic options may be applied and combined for the management of osteoarthritis during the disease [7]. First-line treatment is usually nonpharmacologic, such as weight loss, physical therapy, and exercise programs. These approaches can improve osteoarthritis symptoms and slow disease progression and have no adverse effects when properly applied. In parallel, pharmacologic treatment includes opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and antidepressants [8, 9], which aim to reduce the pain associated with osteoarthritis [10, 11]. However, the adverse effects associated with most of these drugs prevent their long-term use. Besides, because of their potential toxicity, interest in alternative treatments is increasing, and approximately 70% of patients with osteoarthritis are now turning to natural products to alleviate their condition [12].

Natural products to treat osteoarthritis include the symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), which are available as nutritional supplements and oral pharmaceutical-grade products. Two of the more common agents, chondroitin sulfate and glucosamine, are frequently used in the treatment of osteoarthritis. Both agents are biologically active molecules that are substrates for proteoglycan, which is an essential component of the cartilage matrix.

According to the criteria of the European Medicines Agency (EMA), chondroitin can be considered a biologically active substance [13, 14]. Also, these products have been combined in pharmaceutical preparations and food supplements and are recommended by the European League Against Rheumatism (EULAR) and by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [7, 15]. The use and effectiveness of SYSADOAs are controversial issues, although, a study on the perceived effectiveness and safety of these agents revealed that patients report an improvement in mobility, quality of life, and mood and generally considered these drugs to be effective [16].

The purpose of the present review is to examine the safety and effectiveness of SYSADOAs in the treatment of osteoarthritis. Given that the efficacy of SYSADOAs is controversial, the association between quality and origin of the drugs and efficacy is reviewed.

Methods

We performed a review of the literature using the key words oral SYSADOAs, chondroitin sulfate, glucosamine, diacerein, molecular weight, quality, purity, origin, extraction, and quality control. We applied no filters with respect to language or year of publication.

Findings

SYSADOAs

SYSADOAs are slow-acting agents, meaning that their benefits appear some weeks after initiation of treatment and persist after treatment is withdrawn [17].

Two of the more common agents, chondroitin sulphate and glucosamine, exercise a chondroprotective effect and are considered disease-modifying osteoarthritis drugs (DMOADs). Administered alone or in combination, they have a corrective effect on degeneration of connective tissue by supporting new cellular growth in bone and cartilage, as well as by inhibiting cytokines, metalloproteinase activity, and degradative enzymes [18, 19]. As a consequence, they can delay the progression of knee osteoarthritis [18]. In particular, for chondroitin sulfate, the efficacy in decreasing the pain of osteoarthritis and slowing cartilage destruction is clinically meaningful [2], and its use decreases the need for drugs with more harmful adverse effects, such as NSAIDs.

Chondroitin sulfate

Chondroitin sulfate is a glycosaminoglycan that is found in animal cartilaginous tissue and has been recommended for symptomatic pain relief and for improving joint function, with evidence that it delays the progression of osteoarthritis [20]. It is a high-molecular-weight (50-100 kDa), long-chain polymer that can be extracted from various sources (bovine, porcine, or marine cartilage), with bovine being the most effective type [21, 22]. After extraction, its molecular weight is 10-40 kDa. Chondroitin 4-6 sulfate is available as a pharmaceutical-grade product and as a nutritional supplement. The large number of different agents available can hamper prescription of the most appropriate product. Consequently, extrapolation of efficacy data from pharmaceutical-grade chondroitin sulfate to food supplements may be inaccurate depending on the sources and different degrees of purity. The ESCEO specifically recommends pharmaceutical-grade chondroitin sulfate and glucosamine products, since evidence for these agents is robust [7].

In vitro, chondroitin sulfate has immunomodulatory and anti-inflammatory effects: it reduces NF-kB nuclear translocation and decreases production of pro-inflammatory cytokines such as IL-1b, IFN-g, and TNF-a [23]. Moreover, in vitro results indicate that chondroitin sulfate has a chondroprotective effect in osteoarthritis [24]. In their review on evidence for the benefits of pharmaceutical-grade chondroitin sulfate, Hochberg et al [19] reported that this agent exerted a beneficial effect in vitro on the cell types involved in osteoarthritis. Chondroitin sulfate was also shown to increase type II collagen and proteoglycan synthesis in human articular chondrocytes, reduce production of pro-inflammatory factors and proteases, slow the cellular death process, and improve the anabolic/catabolic balance of the extracellular matrix.

Exogenous chondroitin sulfate is absorbed rapidly after oral administration and has been reported to reach peak plasma concentrations after 2.4 hours [25]. As for safety and efficacy, a Cochrane Collaboration systematic review showed that while chondroitin sulfate had small-to-moderate benefits compared with placebo, these were clinically meaningful [26]. Clinical trials confirm that it exerts structure-modifying effects. A meta-analysis published in 2010, reported a small but significant effect of chondroitin sulfate on the reduction in the rate of decline in joint space width of 0.13 mm (95%CI, 0.06-0.19; p=0.0002), which corresponded to an effect size of 0.23 (95%CI, 0.11-0.35; p=0.0001) [27]. Consequently, chondroitin sulfate is classified as a SYSADOA and a DMOAD. The incidence and severity of adverse

effects related to chondroitin sulfate at 1200 mg/d are low, and findings in this respect are similar to those reported for placebo [26, 28].

Michel et al [18] reported that long-term treatment could delay radiographic progression in knee osteoarthritis. Furthermore, in patients with symptomatic osteoarthritis of the hand, chondroitin sulfate was demonstrated to improve hand pain and function and have a good safety profile [29]. Its beneficial effects include anti-inflammatory action, increased type II collagen and proteoglycans, reduced bone absorption, and a better anabolic/catabolic balance in chondrocytes [21].

In their literature review, Honvo et al [30] report that chondroitin had a beneficial effect on pain, symptoms, function, and radiological progression and an excellent safety profile. The CONCEPT trial compared chondroitin sulfate with celecoxib and found that 800 mg/d was superior to placebo and similar to celecoxib for reducing pain and improving function over 6 months in symptomatic knee osteoarthritis. The authors recommend that chondroitin sulfate be considered first-line treatment in the medical management of this condition. In addition, bovine-derived chondroitin sulfate has been shown to suppress osteoclast activity and, therefore, bone resorption at concentrations as low as 1 µg/mL [31]. In fact, in one placebo-controlled trial, chondroitin sulfate was shown to lead to a slight but not significant decrease in pain intensity during activity between weeks 24 and 32 and to be slightly more effective than placebo with respect to quality of life [32]. However, the chondroitin sulfate preparation studied was of avian origin.

Glucosamine

Glucosamine is a monosaccharide that is naturally produced in the human body and can be extracted from crustacean shells. It acts as a substrate for the biosynthesis of glycosaminoglycan chains and the production of aggrecan, which gives cartilage hydrophilicity, thus making it beneficial in osteoarthritis [33]. Glucosamine hydrochloride is a simple molecule that is obtained by extraction and is used as a nutraceutical. Glucosamine sulfate, on the other hand, is obtained semi synthetically. It is found only as a pharmaceutical-grade product (prescription crystalline glucosamine sulfate) [7] and has a stronger inhibitory effect than glucosamine hydrochloride on the cellular processes involved in the physiopathology of osteoarthritis [34].

Glucosamine sulfate inhibits the IL-1 intracellular signaling cascade and gene expression. In vitro, it has been shown to reduce levels of prostaglandin E2 production and interfere with NF-kB DNA binding in chondrocytes and synovial cells [35, 36]. It has also been suggested that

enzymatic breakdown of the extracellular matrix might be reduced with glucosamine. The chondroprotective properties of glucosamine in vivo may be based on the inhibition of catabolic activity and cartilage degradation, as opposed to an ability to rebuild cartilage [37].

The effect of glucosamine sulfate on pain in patients with knee osteoarthritis has been shown to be greater than the effect of paracetamol and similar to that of NSAIDs 7 [7]. In addition, glucosamine sulfate has been shown to have disease-modifying effects [38], to reduce the need for concomitant medication, and to delay the need for total joint replacement surgery [39, 40]. The ESCEO strongly recommends prescription crystalline glucosamine sulfate as Step 1 long-term background therapy in knee osteoarthritis. Herrero-Beaumont et al [41] reported a significant improvement in the Lequesne algofunctional index, as well as in the Osteoarthritis Research Society International (OARSI) responder indices with glucosamine sulfate compared with placebo. The symptomatic benefit of glucosamine has been controversial [34], although a Cochrane review suggested that conflicting trial results could be due to the different formulations of glucosamine studied [42].

Combined chondroitin sulfate and glucosamine

Dietary supplements combining chondroitin sulphate and glucosamine are increasingly popular [43, 44]. However, the paucity of formulations containing both products in their prescription grade makes it difficult to recommend them [7].

In the GAIT trial, Clegg et al [45] reported that combination therapy was effective in a subgroup of patients with moderate-to-severe knee pain. The authors observed that the rate of response was significantly higher with combined therapy than with placebo (79.2% vs 54.3%, p=0.002). The results of another randomized controlled trial [46] indicate that the combination of both agents proved to be as effective as celecoxib in patients with painful knee osteoarthritis. Combination therapy has also been shown to have significant effects on pain relief and function compared with placebo [47].

In a study performed in Australia, Fransen et al [48] analyzed whether glucosamine sulfate, chondroitin sulfate, or the combination of both nutraceutical grade supplements limited or reduced structural disease progression (cartilage loss) or provided pain relief to people with chronic knee pain due to osteoarthritis. While the combination resulted in a statistically significant reduction in joint space narrowing at 2 years, no significant symptomatic benefits were demonstrated compared with placebo. Nevertheless, the authors believe that future

research should examine the combination over longer periods.

Diacerein

Diacerein, also known as diacetylrhein, is an anthraquinone derivative, whose active metabolite is rhein. It displays anti-inflammatory, anti-catabolic, and pro-anabolic properties in cartilage and synovium [49]. Diacerein acts by inhibiting the IL-1b signaling pathway and related downstream metalloproteases [50]. Data from animal models have shown that IL-1b plays a key role in cartilage degradation, subchondral bone remodeling, chondrocyte apoptosis, and joint inflammation [51]. In animal models, diacerein has been very effective in the prevention of cartilage destruction and may have disease-modifying properties in individuals with hip and knee osteoarthritis [52]. It also has a protective effect against subchondral bone remodeling [53]. In a rabbit model of surgically induced knee osteoarthritis, diacerein elicited an anti-inflammatory effect on the synovial membrane and modified the orientation of the subchondral trabecular lattice [54].

Evidence from clinical trials indicates that diacerein could provide effective symptomatic relief in patients with osteoarthritis. Pelletier et al [55] found diacerein to be superior to placebo at 100 mg/day with respect to pain on movement. Similarly, data from the ECHODIAH trial [52] showed that diacerein was superior to placebo in terms of its structure-modifying effect and radiographic progression in patients with hip osteoarthritis. The OARSI recommendations report that diacerein was more efficacious for pain reduction than paracetamol in patients with osteoarthritis [56]. As for NSAIDs, while their onset of action is more rapid than that of diacerein, their efficacy with respect to joint function and pain was comparable to that of diacerein after 1 month of treatment [49].

The incidence of adverse events with diacerein was similar to that of piroxicam; however, the percentage of patients with adverse events in the piroxicam group was higher for dyspepsia (32.9% vs 22.1%) and edema (9.4% vs 4.7%) [57]. Diacerein has been associated with a higher risk of diarrhea, especially in long-term therapy, although this is generally considered to be mild to moderate. It has also been shown to induce rash, pruritus, eczema, and a mild/moderate increase in liver enzymes. Few severe events have been recorded [49].

All in all, compared with NSAIDs, diacerein seems to have similar efficacy and an acceptable safety profile in patients with knee osteoarthritis. The ESCEO considers diacerein to be a first-line pharmacological background treatment in this condition [49]. It could prove particularly interesting in patients with known upper gastrointestinal problems or heart disease, for whom NSAIDs are contraindicated [58].

Relationship between quality and efficacy/safety

Preparations of glucosamine and chondroitin sulfate could vary considerably, with the result that use of incorrect formulations could result in suboptimal outcomes, in turn leading to poor adherence and dissatisfaction with treatment. [66] According to the ESCEO recommendations, clinical benefit, adherence, and satisfaction can only be ensured through a judicious choice of formulation. The patented prescription-grade crystalline glucosamine sulfate is formulated in a stabilized delivery system, which maximizes bioavailability in humans and has been shown to reverse the pro-inflammatory and degenerative effects on cartilage. In their review of the literature, Vlad et al [67] assessed studies on glucosamine to investigate potential sources of heterogeneity and found that the results reported for the efficacy of glucosamine hydrochloride in knee osteoarthritis are markedly heterogeneous, thus making it difficult to draw definitive conclusions, probably due, in part, to differences in the formulations. The importance of the formulation was highlighted in an analysis of trials based on the patented formulation. The authors examined randomized clinical trials evaluating the effectiveness and safety of glucosamine in osteoarthritis based on various indexes (WOMAC, Lequesne index), which showed that a commercial preparation of glucosamine was superior to placebo with respect to pain and function [42].

Quality

The biological activity of nutritional supplements and pharmaceutical-grade products can vary considerably owing to current regulatory restrictions [2, 59].

Quality and consistency issues have arisen with chondroitin sulfate as a food supplement, and these have important implications for efficacy and safety. Wide variations have been reported between the labeled amount of chondroitin sulfate and the amount actually present in the product [60, 61], possibly as a result of factors such as source material, manufacturing processes, and contaminants. In their quantitative and qualitative evaluation of chondroitin sulfate in dietary supplements based on a very high pure European Pharmacopeia chondroitin sulfate reference standard, Volpi and Maccari [60] found that the content of chondroitin sulfate in finished products evaluated using 2 validated methods (agarose gel electrophoresis

and SAX-HPLC) was almost 100% and that it met the label claim, although the molecular weight and the disaccharide content varied by about 30%. Adebowale et al [43] found that only 5 of 32 tested supplements contained ±10% of the labeled amount, and that 17 of 32 contained less than 40% of the label claim.

Data from well-designed studies on pharmaceutical-grade chondroitin sulfate should not be extrapolated to food supplements, and vice versa [2]. When the drug is supplied as a food supplement or nutraceutical, its quality may not match that of the pharmaceutical-grade product due to the absence of controls. In vitro studies analyzing the composition of chondroitin sulfate using various techniques revealed variations in molecular weight depending on the origin of the product [62, 63] and in disaccharide content [64, 65]. Variations in origin, production, and purification processes can lead to differences in biological effects [63]. Cantley et al [31] showed that the effects of bovine-derived chondroitin sulfate were more consistent than those of fish- and pig-derived products.

The purification process involves a certain degree of degradation, which reduces the molecular weight of the product. While the objective of the purification protocol is to minimize contaminants (eg, other glycosaminoglycans, proteins, small organic molecules, viruses, prions, and solvents) [21], the extraction and purification conditions can have a critical effect on molecular mass, which is associated with pharmacological activity [60]. Therefore, accurate and practical analytical methods are necessary to ensure quality control of these products.

Discussion

SYSADOAs encompass a heterogeneous group of drugs with a long-term effect on the symptoms of osteoarthritis. Their use in clinical practice is a controversial issue, often depending on the specific type of patient and associated comorbidities, on the severity of knee and hand osteoarthritis, and on the characteristics of the product used. The case of nutraceuticals (food supplements) is even more controversial, given loose research requirements and regulation in production standards. The variations in the extraction and purification techniques can lead to differences in content, composition, purity, biological effects, and safety [21]. Consequently, many preparations are of poor quality, contain amounts that differ from those shown on the label, and do not provide information on the structural characteristics or mass [68]. However, in the absence of data from clinical trials, we cannot state that nutraceuticals are effective or not.

One of the main criticisms of SYSADOAs is that their symptom-modifying effects are mild or insignificant. Guidelines do see a clear role for SYSADOAs in the management of knee osteoarthritis, and partially in hand osteoarthritis. In their updated stepwise treatment algorithm, the ESCEO considers long-term administration of SYSADOAs, specifically pharmaceutical-grade glucosamine sulfate and/or chondroitin sulfate, as suitable therapy for symptomatic disease, stating that the evidence for this approach is “unequivocal” [7]. However, long-term treatment with chondroitin sulfate has been reported to exert a disease-modifying effect by delaying radiographic progression in patients with knee osteoarthritis [18, 68], and patients perceive these drugs to be effective [16].

In their 2019 update on the role of pharmaceutical-grade chondroitin sulfate for symptomatic management of knee osteoarthritis, Honvo et al [30] report that chondroitin sulfate consistently demonstrated a beneficial effect on pain and function with an excellent safety profile and cost-effectiveness. When evaluating safety and efficacy, it is important to ensure that data are interpreted taking into account differences between pharmaceutical-grade products and nutraceutical-grade products and that the

source and purity of the preparation under investigation are clearly stated [2]. Given the different physicochemical characteristics and the lack of clinical studies, the risk-benefit of nutraceutical-grade preparations cannot be extrapolated from pharmaceutical-grade products [14]. However, despite differences observed in vitro, a pharmaceutical-grade SYSADOA has never been shown to be better than a nutraceutical, simply because no comparative studies have been performed in humans.

In order to shed some light on the controversy surrounding SYSADOAs, further studies are required to reveal subgroups of patients who are more likely to benefit from this approach, as well as other functions of chondroitin sulfate. Furthermore, results from studies investigating the structure-modifying properties of these agents could lead to the design of better, more effective products [68]. Much of the controversy surrounding SYSADOAs arises as a result of differences in quality, purity, and efficacy. It would be interesting to perform clinical trials that specifically compare pharmaceutical-grade products with nutraceuticals based on an assessment of these factors. No randomized double-blind studies have shown that the combination of pharmaceutical-grade chondroitin sulfate and glucosamine can be substituted by other formulations found as nutraceuticals.

Indeed, differences in quality between nutraceuticals can be observed not only between products, but also between batches of the same product [69], and the lack of clear regulatory definitions on content makes it very difficult to guarantee quality. The quality and purity of pharmaceutical-grade formulations of SYSADOAs are generally high, whereas those of nutraceuticals are often controversial or demonstrably poor. Consequently, closer regulation of manufacturers is necessary to ensure that only high-quality nutraceuticals are manufactured. In addition, purity should be guaranteed with the use of specific and accurate analytical procedures [61].

Abbreviations

NSAID, nonsteroidal anti-inflammatory drug
SYSADOA, symptomatic slow-acting drugs for osteoarthritis
EMA European Medicines Agency
EULAR, European League Against Rheumatism
ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
DMOAD, disease-modifying osteoarthritis drugs
OARSI, Osteoarthritis Research Society International

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Authors' Contributions

JV, IM, and MV contributed to the study conception and design. MV performed the literature research and wrote the first draft of the manuscript. JV and IM read and comment on the first draft of the manuscript. JV, IM and MV prepared the final version of the manuscript. All authors read and approved the final version of the manuscript.

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