Understanding Glucosamine and Chondroitin

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Chelsey McIntyre, PharmD, is a clinical pharmacist who specializes in drug information, literature analysis, and medical writing. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017, after which she spent the next six years as a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She continues to create rigorous professional analysis and patient education materials for various publications while also practicing as a hospital pharmacist. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care.

Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals whose patients are taking or are interested in taking glucosamine and/or chondroitin supplements.

Accreditations & Approvals

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INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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A complete Works Cited list begins on page 10.

Mention of commercial products does not indicate endorsement.

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NetCE designates this continuing education activity for 1.5 ANCC contact hours.

IPCE CREDIT™

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Individual State Nursing Approvals

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of glucosamine and chondroitin.

Learning Objectives

Upon completion of this course, you should be able to:

1. Identify and describe the forms of glucosamine and chondroitin available on the market.
2. Review the evidence for the use of glucosamine and chondroitin for common conditions.
3. Discuss the potential safety concerns with glucosamine and chondroitin.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

AN OVERVIEW OF GLUCOSAMINE

Glucosamine is an amino sugar that is produced naturally in humans. It is necessary for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (mucopolysaccharides). These compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, blood vessels, heart valves, and structures of the eye. The broad presence of these compounds throughout the human body has led to wide-ranging interest in the use of glucosamine for various health purposes.

GLUCOSAMINE SUPPLEMENTS

Glucosamine supplements are available in three different salt forms: glucosamine sulfate, glucosamine hydrochloride, and *N*-acetyl glucosamine. The glucosamine base used in supplements has most commonly been derived from the exoskeletons of shellfish, such as shrimp, lobster, and crabs. However, glucosamine can also be created synthetically or obtained from *Aspergillus* or fermented corn [1].

Glucosamine Sulfate

Glucosamine sulfate is the most common supplemental form of glucosamine. This form must be created semi-synthetically in a lab [1]. Glucosamine sulfate is inherently unstable and must be stabilized with a salt moiety. This typically involves the use of sodium chloride, but potassium chloride may also be used [3].

Many different manufacturers produce glucosamine sulfate supplements, but not all of these products have been evaluated in clinical research. Of the products that have been studied, some demonstrate stronger benefits than others, suggesting variability in product quality and purity. In fact, analyses of products available in Europe and the United States suggest that many supplements contain less than 90% of labeled content, and some glucosamine sulfate products actually contain glucosamine hydrochloride with added sulfate [1].

Glucosamine Hydrochloride

Glucosamine hydrochloride (HCl) is the second most common supplemental form of glucosamine. This salt occurs naturally and can be obtained from shellfish, fungi, or corn via a simple extraction process.

Many different manufacturers produce glucosamine hydrochloride supplements, but not all of these products have been evaluated in clinical research. Of the products that have been studied, some demonstrate stronger benefits than others, suggesting variability in product quality and purity.

N-Acetyl Glucosamine

N-acetyl glucosamine, the acetylated derivative of glucosamine, is the least common form found in supplements. This form of glucosamine has not been extensively studied in clinical research; most of the evidence around the use of glucosamine supplements is for the sulfate and hydrochloride salts [5].

AN OVERVIEW OF CHONDROITIN

Chondroitin sulfate is a glycosaminoglycan found naturally in the body, particularly in connective tissues. It is a very large molecule; the species or tissue of origin, as well as the extraction method used, can affect its final size [1].

Unfortunately, many chondroitin sulfate supplements available on the market have been shown to have inconsistent potency and quality, with actual chondroitin sulfate content ranging from 0% to 115% of what is stated on the label [4]. Additionally, although most chondroitin sulfate products claim to be derived from bovine tissue, analyses of available products have found chondroitin obtained from multiple sources, regardless of what is stated on the label. These include mixed animal sources and mixed animal and marine sources [6].

THIRD-PARTY QUALITY CERTIFICATION

To ensure the selection of a high-quality product, look for third-party quality certification stamps, such as those from USP or NSF.

USP

The United States Pharmacopeia (USP) is typically considered the criterion standard for dietary supplement quality verification. In addition to inspecting manufacturing facilities for compliance with Good Manufacturing Practices (GMP) at least two times in a three-year period, USP will also conduct random off-the-shelf analyses of verified products to ensure that the contents of the product match those listed on the label. This random testing holds manufacturers to a high standard. The USP verification stamp can be found on a product's label.

NSF

NSF is also a strong source of dietary supplement quality verification. However, general NSF certification does not necessarily imply the same quality standards as those seen with USP verification. In order for a manufacturer to list NSF certification on their website, they must pass an NSF inspection of cGMP compliance every six months. However, NSF does not conduct off-the-shelf analyses of products unless the manufacturer is enrolled in the "Contents Tested and Certified" or "Certified for Sport" programs. Under these programs, manufacturers are subject to random off-the-shelf testing and can place an NSF seal of approval on the product label. That seal of approval will typically state "NSF: Contents Certified" or "NSF: Certified SPORT."

REVIEWING THE EVIDENCE

GLUCOSAMINE AND CHONDROITIN FOR OSTEOARTHRITIS

Extensive research has been conducted on the use of glucosamine or chondroitin, alone or in combination, for the management of osteoarthritis. However, the findings differ with each product and salt form.

Glucosamine Sulfate

Most research has focused on the use of oral glucosamine sulfate for the management of knee osteoarthritis. A very limited amount of research has been conducted in hip and spine osteoarthritis, with inconclusive findings [7].

When used for knee osteoarthritis, meta-analyses of the available research show that taking glucosamine sulfate 1,500 mg daily for up to three years modestly improves pain and function when compared with placebo. Individual studies have shown a 28% to 41% pain reduction and 21% to 46% improvement in function [3; 8; 9; 10; 11; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30].

Small studies comparing glucosamine sulfate with nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen 400 mg three times daily or piroxicam 20 mg daily, suggest that these treatments provide similar benefit. However, NSAIDs appear to relieve symptoms within two weeks, whereas glucosamine sulfate can take four to eight weeks [12; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30].

The benefits of glucosamine sulfate seem to vary depending on the product used. As mentioned previously, glucosamine products have been associated with quality and potency concerns.

To date, the most consistent positive evidence for glucosamine sulfate has been seen with Dona, a specific crystalline glucosamine sulfate product that has been sold as a prescription in some countries and is thus often referred to as "pharmaceutical-grade." In fact, some studies with this product have shown that it can prevent joint space narrowing of greater than 0.5 mm by up to 54% when compared with placebo. Studies using other glucosamine sulfate products have yielded conflicting findings related to disease progression [1; 13; 15].

There is currently a significant amount of debate as to whether the benefit seen with this product is due to bias introduced by industry funding or due to a truly higher quality product. This formulation of glucosamine sulfate is claimed to have superior bioavailability versus other forms of glucosamine, but pharmacokinetic evidence in support of this claim is limited.

Glucosamine Hydrochloride

In contrast to the generally positive findings related to the use of glucosamine sulfate for knee osteoarthritis, glucosamine hydrochloride has shown no real benefit in clinical research.

A meta-analysis of the available research shows that taking glucosamine hydrochloride 1,500 mg daily for up to 18 months does not seem to reduce pain when compared with placebo. Research on the use of glucosamine hydrochloride in combination with chondroitin sulfate has yielded conflicting findings. Some research has found that taking this combination is non-inferior to celecoxib 200 mg daily for relieving pain, but not for improving stiffness or function. Other research has shown no benefit. It is possible that any benefit identified from this combination may be due to chondroitin sulfate [15; 24; 31; 32; 33; 34].

Although the research indicates that glucosamine hydrochloride is less effective than glucosamine sulfate for the management of knee osteoarthritis, head-to-head trials comparing these two salt forms are lacking. It has been proposed that the bioavailability of glucosamine from glucosamine hydrochloride may be reduced in comparison to pharmaceutical-grade crystalline glucosamine sulfate, but more research is needed to confirm [15; 24; 31; 32; 33; 34].

N-Acetyl Glucosamine

This salt form has not been evaluated for use in osteoarthritis and should not be recommended. There is some speculation that *N*-acetyl glucosamine is more effective for stimulating the production of hyaluronic acid than other forms of glucosamine, but further research is needed to confirm the clinical relevance of this hypothesis [5].

Chondroitin Sulfate

Chondroitin sulfate, when taken alone, has demonstrated modest benefit for reducing pain and improving function in some patients with knee osteoarthritis. Meta-analyses of the available research show that taking chondroitin sulfate 800–2,000 mg in single or divided doses daily for at least three months can modestly reduce pain and disability when compared with placebo [11; 22; 23; 30; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46]. Some research has suggested that the number needed to treat for one patient to experience at least a 20% reduction in pain may be as high as 16.

Some studies also suggest that chondroitin sulfate may have disease-modifying benefits. Clinical research in adults with osteoarthritis of the knee or hip shows that taking chondroitin sulfate daily at a dose of at least 800 mg for two years might modestly reduce joint degeneration and narrowing when compared with placebo or celecoxib [11; 22; 23; 30; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46].

The most positive findings with chondroitin sulfate have involved the use of pharmaceutical-grade products that are available as prescription in other countries, such as Chondrosulf (IBSA Institute Biochimique SA), Chondrosan (Bioibérica, S.A.), and Structum (Laboratoires Pierre Fabre). Due to their availability as prescription products in some countries, these products are also sometimes referred to as "pharmaceutical grade" [47; 48].

As with glucosamine sulfate, there is a significant amount of debate as to whether the benefits seen with these products are due to bias introduced by industry funding or due to truly higher quality. However, these products are not readily available for purchase in the United States.

Glucosamine Sulfate and Chondroitin Sulfate Combinations

Many supplement products available on the market provide glucosamine and chondroitin in combination. Although most evidence evaluating glucosamine sulfate or chondroitin sulfate alone suggests modest benefit for knee osteoarthritis, research on the use of combination products is less conclusive [11; 23; 30; 49; 50; 51]. Some long-term studies in patients with osteoarthritis show that taking chondroitin sulfate and glucosamine sulfate together modestly reduces joint space narrowing when compared with a control group [16; 23; 30; 49; 50; 51].

However, not all research is positive. Some individual clinical studies, as well as meta-analyses of the available research, have not shown a reduction in pain in patients taking chondroitin sulfate in combination with either glucosamine hydrochloride or glucosamine sulfate [23].

Many of the available meta-analyses on these combination products have pooled research evaluating both glucosamine sulfate and glucosamine hydrochloride together. The differing benefits seen when these salt forms are studied alone limits the applicability of the findings from these analyses [11; 16; 49; 50; 51].

Additionally, limited pharmacokinetic research has suggested that chondroitin sulfate may interfere with the absorption of glucosamine. Although this may help to explain some of the inconsistent study outcomes, further research is needed to confirm this finding.

Glucosamine and Chondroitin in the Guidelines

The place of glucosamine and chondroitin in clinical practice is unclear. In fact, clinical guidelines provide conflicting recommendations.

The American College of Rheumatology (ACR) strongly recommends against the use of any glucosamine or chondroitin products for any form of osteoarthritis. The European Society of Clinical and Economic Aspects of Osteoarthritis (ESCEO) strongly recommends for the use of pharmaceutical-grade glucosamine sulfate or chondroitin sulfate products in patients with osteoarthritis. The ESCEO also provides a weak recommendation against the use of glucosamine and chondroitin in combination [52; 53].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American Academy of Orthopaedic Surgeons, glucosamine and/or chondroitin may be helpful in reducing pain and improving function for patients with mild-to-moderate knee osteoarthritis; however, the evidence is inconsistent/limited, and additional research clarifying the efficacy of each supplement is needed.

(https://journals.lww.com/jaaos/Fulltext/2022/05010/AAOS_Clinical_Practice_Guideline_Summary_.10.aspx. Last accessed October 31, 2022.)

Strength of Recommendation: Limited

These conflicting recommendations are related to differing interpretations of the previously discussed evidence. The ACR has determined that the positive benefits identified in industry-funded studies evaluating pharmaceutical-grade products, as opposed to the conflicting findings identified with other products, indicates the introduction of industry bias [52].

The ESCEO, on the other hand, has determined that the positive benefits identified in industry-funded studies evaluating pharmaceutical-grade products is due to the higher quality and bioavailability of the products used [1; 53].

Considering the conflicting guidance, the decision to recommend glucosamine sulfate or chondroitin sulfate for osteoarthritis should be made on an individual basis and should consider each patient's preferences and risk factors. Products that carry a third-party quality certification should be recommended to minimize concerns related to product quality and potency.

GLUCOSAMINE AND CHONDROITIN FOR OTHER FORMS OF JOINT PAIN

There has been interest in using glucosamine and/or chondroitin for various forms of joint pain other than osteoarthritis. However, research remains limited and inconclusive.

Studies evaluating the use of glucosamine sulfate, glucosamine hydrochloride, or *N*-acetyl glucosamine for the management of non-osteoarthritic knee pain have shown minimal or no benefit. Similarly, research on the use of glucosamine for temporomandibular disorder (TMD) is limited to two small, conflicting studies [5; 14].

There is also interest in the use of glucosamine sulfate and chondroitin sulfate for aromatase inhibitor-induced arthralgia. However, the available research is limited to one small, open-label, uncontrolled study that suggested only modest benefit [54].

GLUCOSAMINE FOR OVERALL HEALTH

Some observational research has suggested that regular use of glucosamine is associated with a modest reduction in risk for type 2 diabetes and fatal and nonfatal cardiovascular events, such as coronary heart disease and stroke [55; 56; 57; 58; 59; 60]. Unfortunately, these studies have not clarified the form of glucosamine used, nor the dose, frequency, or duration of use. Furthermore, the adults that reported use of glucosamine also reported overall healthier lifestyle habits than those that were not taking glucosamine. Although these studies attempted to control for these differences, higher quality, prospective research is still needed to clarify the relationship, if any, between glucosamine and long-term health outcomes [55; 56; 57; 58; 59; 60].

Another observational study has suggested that regular use of glucosamine with chondroitin for at least one year is associated with a reduced incidence of overall mortality. However, this study has the same weaknesses and deficiencies as those showing a reduced risk for diabetes and cardiovascular disease [55; 56; 57; 58; 59; 60].

SAFETY CONSIDERATIONS

GLUCOSAMINE

Glucosamine sulfate and glucosamine hydrochloride have been used extensively in clinical research, with minimal reported adverse effects. When used in doses of up to 1,500 mg daily for up to two to three years, these salt forms appear to be safe for most adults [61; 68; 69].

Adverse Effects

The most frequently reported adverse effects include bloating, constipation, cramps, diarrhea, heartburn, and nausea. In the past, there have been concerns regarding the potential for glucosamine to increase insulin resistance, blood pressure, and blood lipids. However, most research suggests that these concerns are unfounded, and that glucosamine does not have an adverse impact on these parameters [62; 63; 64; 65; 66; 67; 68; 69].

Allergies

There have been multiple reports of hypersensitivity reactions with the use of glucosamine. In one report of glucosamine-related adverse events in Australia, 35% of hypersensitivity reactions were classified as mild, 49% as moderate, and 16% as severe, with 1.5% of cases involving anaphylaxis [68; 69].

Glucosamine is commonly derived from the exoskeletons of shrimp, lobster, and crabs. Thus, there is concern that the risk for hypersensitivity reactions to glucosamine may be greater in those with shellfish allergy [1].

Shellfish allergies are caused by IgE-mediated reactions to antigens found in shellfish meat, not the exoskeleton. However, it is possible that allergen contamination can occur during manufacturing. Until more is known, use glucosamine with caution in these patients [1].

Interactions

Multiple reports, including more than 40 cases reported to the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO), suggest that glucosamine might increase the international normalized ratio (INR) in patients who are also taking warfarin. The reason for such an interaction is unclear. Until more is known, use glucosamine with caution in patients who are taking warfarin. For those patients who initiate glucosamine treatment, consider increased INR monitoring [1].

CHONDROITIN SULFATE

Chondroitin sulfate has been evaluated extensively in clinical research, with limited reports of adverse effects. When used in a dose of up to 2,000 mg daily for up to six years, it appears to be safe for most adults [61].

Adverse Effects

The most frequently reported adverse effects include abdominal pain, bloating, constipation, diarrhea, heartburn, and nausea.

Interactions

Chondroitin sulfate, in combination with glucosamine, has been implicated in a small number of case reports of elevated INR in patients taking warfarin. However, it has not been reported to cause INR elevation when used without glucosamine. At this time, it is unclear if chondroitin sulfate alone can increase the risk for bleeding in patients taking warfarin; use with caution.

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of dietary supplements be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter.

CONCLUSION

Glucosamine and chondroitin are generally safe for most adults. Specific formulations and products may be beneficial for improving symptoms of knee osteoarthritis, although there continues to be some debate as to the reliability of the evidence. Also, certain patients should be cautious with the use of these substances.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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