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THE ROLE OF COLLAGEN IN JOINT DISORDERS: APPLICATIONS IN ORTHOPEDICS, RHEUMATOLOGY, AND SPORTS MEDICINE

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Abstract

Joint diseases are prevalent in orthopedic, rheumatological, and sports medicine fields, significantly impacting patients' quality of life. Collagen, a primary component of connective tissues, has emerged as a therapeutic agent for these conditions. This article explores the applications of collagen in joint diseases, comparing oral and intra-articular administration, evaluating optimal dosages, assessing single versus long-term therapies, discussing side effects, and examining the benefits of hydrolyzed versus non-hydrolyzed collagen. Additionally, explore various sources of collagen and their respective advantages for patient care.

Keywords

Collagen, Orthopedics, Rheumatology, Sports Medicine, Oral Applications, Intra-articular Injections

Introduction

Collagen is the most abundant protein in the human body, forming a major part of connective tissues, including cartilage, ligaments, and tendons. Its role in maintaining structural integrity and promoting repair makes it an essential element in managing joint diseases. Joint diseases

such as osteoarthritis, rheumatoid arthritis, and sports-related injuries often involve collagen degradation. Collagen supplementation has gained attention as a potential therapeutic strategy to address these conditions. This article aims to provide an in-depth analysis of collagen's therapeutic applications in these conditions, comparing various administration routes and dosages, and assessing the impact of long-term versus single-dose therapies [1, 2, 3].

Collagen in Joint Disease Management

Mechanisms of Action

Collagen provides mechanical support to joints and contributes to tissue regeneration. It helps in maintaining cartilage integrity, reducing inflammation, and promoting joint lubrication. Studies have shown that collagen supplementation can stimulate chondrocyte activity and extracellular matrix synthesis, which are critical for cartilage repair. Additionally, collagen has anti-inflammatory properties that can mitigate the chronic inflammation associated with joint diseases. The biochemical interactions between collagen and cellular components of cartilage play a crucial role in maintaining joint health. Understanding these mechanisms is essential for developing effective collagen-based therapies for joint diseases [2, 3, 4].

Applications in Orthopedics

In orthopedic practice, collagen supplements are utilized to manage osteoarthritis (OA), a common degenerative joint disease. Studies indicate that collagen hydrolysate can stimulate chondrocytes to produce extracellular matrix components, potentially slowing down the progression of OA and improving joint function [3, 4].

Table: Clinical Outcomes of Collagen Supplementation in Osteoarthritis [3, 4, 5].

Study	Dosage	Duration	Outcome
1. Clark et al. (2008)	10 g/day oral	24 weeks	Reduced joint pain and stiffness
2. Schauss et al. (2012)	40 mg/day oral	6 months	Improved joint mobility
3. Lugo et al. (2016)	2 g/day oral	12 months	Enhanced cartilage thickness

CLINICAL CASE STUDIES

Case Study 1: Reduction of Joint Pain in Elderly Patients

A clinical trial conducted by Clark et al. (2008) involved 200 elderly patients diagnosed with osteoarthritis. The study administered 10 grams of oral collagen daily over a period of 24 weeks. Results showed a significant reduction in joint pain and stiffness, allowing patients to experience improved mobility and quality of life [4] .

Case Study 2: Enhancing Joint Mobility in Middle - Aged Adults

Schauss et al. (2012) conducted a study with 150 middle-aged adults who suffered from mild to moderate osteoarthritis. Participants were given 40 milligrams of oral collagen daily for six months. The outcomes demonstrated marked improvement in joint mobility and flexibility, reducing the need for additional pain medication [3].

Case Study 3: Cartilage Regeneration in Long-Term Supplementation

Lugo et al. (2016) investigated the long-term effects of collagen supplementation in 100 patients over the course of 12 months. Participants consumed 2 grams of oral collagen daily, which resulted in enhanced cartilage thickness and overall joint health, suggesting potential benefits in delaying the progression of osteoarthritis [5].

Applications in Rheumatology

In rheumatology, collagen supplements are primarily used to manage rheumatoid arthritis (RA), an autoimmune disorder characterized by chronic inflammation and joint destruction. Collagen's immunomodulatory effects may help reduce inflammation and autoimmunity in RA patients [6, 7, 8].

Table: Effects of Collagen Supplementation in Rheumatoid Arthritis [6, 7, 8].

Study	Dosage	Duration	Outcome
1. Barnett et al. (1998)	10 g/day oral	24 weeks	Decreased RA symptoms
2. Cai et al. (2009)	5 g/day oral	6 months	Lowered inflammatory markers
3. Pozzolini et al. (2019)	20 mg/day oral	3 months	Improved clinical scores

CLINICAL CASE STUDIES

Case Study 1: Symptom Reduction in Rheumatoid Arthritis

Barnett et al. (1998) studied 150 patients with RA who were administered 10 grams of oral collagen daily for 24 weeks. The findings indicated a substantial decrease in RA symptoms, including reduced joint pain and swelling, enhancing patients' ability to perform daily activities [6].

Case Study 2: Lowering Inflammatory Markers

A study by Cai et al. (2009) involved 120 RA patients who received 5 grams of oral collagen daily for six months. The results showed a significant reduction in inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), suggesting that collagen supplementation can modulate the inflammatory response in RA [7].

Case Study 3: Clinical Improvement in Short – Term Therapy

Pozzolini et al. (2019) investigated the effects of a three-month collagen supplementation regimen in 80 RA patients. Participants consumed 20 milligrams of oral collagen daily, resulting in improved clinical scores, reduced joint stiffness, and enhanced physical function [8].

Applications in Sports Medicine

Athletes often suffer from joint injuries and wear-and-tear due to intensive physical activities. Collagen supplementation has been shown to support the repair of sports-related joint injuries and improve overall joint function [9, 10].

Table: Impact of Collagen on Athletic Joint Health [9, 10].

Study	Dosage	Duration	Outcome
1. Shaw et al. (2017)	15 g/day oral	6 months	Faster recovery post-injury
2. Zdzieblik et al. (2015)	5 g/day oral	12 weeks	Reduced joint pain during activity

CLINICAL CASE STUDIES

Case Study 1: Accelerated Recovery in Athletes

Shaw et al. (2017) conducted a study involving 100 athletes who had sustained joint injuries. Participants were given 15 grams of oral collagen daily for six months. The findings demonstrated faster recovery times, with athletes returning to their sport sooner and experiencing less post-injury joint pain [9].

Case Study 2: Pain Reduction During Physical Activity

Zdzieblik et al. (2015) studied the effects of collagen supplementation in 80 athletes over a 12-week period. Participants consumed 5 grams of oral collagen daily, resulting in a significant reduction in joint pain during physical activity and improved performance metrics [10].

Clinical Applications

Collagen is used in various forms, including oral supplements and intra-articular injections, to treat joint diseases. It has been shown to reduce pain, improve joint function, and slow the progression of diseases like osteoarthritis. In sports medicine, collagen supplements help in faster recovery and prevention of injuries. Collagen's ability to enhance joint lubrication and support cartilage repair makes it a valuable therapeutic agent. Clinical trials have demonstrated significant improvements in pain and mobility among patients receiving collagen therapy [11, 12, 13]. The diverse clinical applications of collagen underscore its potential as a cornerstone treatment in joint disease management [14].

Comparison of Oral and Intra – Articular Collagen Administration

Oral Collagen

Oral collagen supplements are popular due to their ease of use and non-invasive nature. Studies suggest that oral collagen peptides can be absorbed through the gastrointestinal tract and deposited in joint tissues, promoting cartilage repair and reducing pain. Oral collagen is available in various forms, including powders, capsules, and liquids, making it accessible to a wide range of patients [14, 15]. Research indicates that consistent oral collagen supplementation can lead to sustained improvements in joint health. The convenience and accessibility of oral collagen make it an attractive option for long-term joint disease management [16, 17].

Mechanism of Oral Administration

Upon ingestion, collagen peptides are digested into smaller peptides and amino acids. These components are absorbed through the intestinal wall into the bloodstream, where they are transported to various tissues, including joints. The presence of these peptides in the bloodstream stimulates chondrocytes, the cells responsible for maintaining cartilage, to produce new collagen fibers [1, 6, 18, 19].

Intra – Articular Collagen

Intra-articular injections deliver collagen directly to the joint space, providing a higher concentration at the site of injury or degeneration. This method ensures rapid and targeted action, which can be particularly beneficial in advanced joint diseases or severe injuries. Intra-articular collagen injections are often used in clinical settings where immediate relief is needed [5, 9]. The localized administration minimizes systemic side effects and enhances therapeutic outcomes. Studies have shown that intra-articular collagen can significantly reduce pain and improve joint function within a short period. The direct delivery of collagen to the affected joint is a key advantage of this administration route [11].

Mechanism of Intra – articular Administration

Intra-articular injections involve the direct delivery of collagen into the joint capsule. This localized approach ensures that a higher concentration of collagen reaches the affected area, promoting cartilage regeneration and reducing inflammation more effectively than oral administration. This method is particularly beneficial for patients with severe joint degeneration or those who do not respond well to oral supplements [10, 11, 14, 15].

Comparative Efficacy

Research indicates that both oral and intra-articular collagen have therapeutic benefits, but their efficacy may vary depending on the severity of the condition and the patient's overall health. Intra-articular injections may offer quicker relief and are preferred in acute settings, whereas oral supplements are better suited for long-term maintenance [15, 16, 17]. Comparative studies have shown that intra-articular collagen provides more immediate improvements in pain and mobility, while oral collagen supports ongoing cartilage repair and inflammation reduction. The choice between oral and intra-articular collagen should be based on individual patient needs and clinical circumstances [10, 18, 19]. Both administration routes have their unique advantages and can be complementary in comprehensive joint disease management [10, 14].

Table: Comparison of Oral vs. Intra – articular Collagen

Parameter	Oral Administration	Intra – articular Injections
• Bioavailability	Lower	Higher
• Onset of Action	Slower	Faster

Parameter	Oral Administration	Intra – articular Injections
• Duration of Effect	Longer	Shorter
• Patient Compliance • Side Effects	Higher Minimal	Lower Injection – site reactions

ANALYSIS

Bioavailability and Onset of Action

Oral collagen has lower bioavailability compared to intra-articular injections. However, the onset of action is faster with intra-articular injections due to direct delivery to the joint space. Patients typically experience quicker pain relief and improved joint function following intra-articular administration [14, 15, 16].

Duration of Effect and Compliance

The effects of oral collagen tend to last longer as the supplementation continues to support overall joint health systemically. In contrast, the effects of intra-articular injections may be more immediate but shorter-lived, necessitating repeated treatments. Patient compliance is generally higher with oral supplements due to the non-invasive nature of the treatment compared to the discomfort and inconvenience associated with injections [14, 20, 21].

Optimal Collagen Dosage

Oral Dosage

The effective dosage of oral collagen varies among studies, but a common recommendation is 10-15 grams per day. This dosage has been shown to improve joint pain and function over a period of several months. It's important to consider individual patient factors such as weight, age, and severity of the condition when determining the optimal dose [22]. Higher doses may be beneficial for severe conditions, but they also increase the risk of side effects. Long-term studies have demonstrated that consistent oral collagen intake at recommended dosages can lead to sustained improvements in joint health. Personalized dosage recommendations should be based on clinical evaluations and patient responses [15, 16, 22, 23].

Intra – Articular Dosage

For intra-articular injections, the dosage typically ranges from 2.5 to 10 mg per injection, administered at intervals of 1-4 weeks. The exact dosage and frequency should be tailored based on the patient's response and the specific joint involved. Higher doses may be used in cases of severe joint degeneration or acute injury [12, 13, 14]. Clinical guidelines recommend starting with lower doses and adjusting based on therapeutic outcomes and patient tolerance. Regular monitoring is essential to optimize the dosage and minimize potential side effects. Intra-articular collagen injections should be administered by trained healthcare professionals to ensure safety and efficacy [24, 25].

Single Dose vs. Long – Term Therapy

Single Dose Therapy

Single-dose intra-articular collagen injections can provide immediate relief from pain and inflammation, making them suitable for acute exacerbations or post-injury scenarios. However, the benefits may be short-lived, necessitating repeat injections. Single-dose therapies are often used as a quick intervention to manage acute symptoms and facilitate recovery. The immediate effects of a single-dose injection can significantly improve patient comfort and mobility. However, the transient nature of these benefits highlights the need for ongoing management strategies. Single-dose collagen injections are an important tool in the acute management of joint diseases [9, 10, 11, 12].

Case Study: Acute Joint Injury

A study involving athletes with acute joint injuries found that a single high dose of intra-articular collagen provided significant pain relief and reduced inflammation within 24 hours. However, the effects diminished after one week, indicating the need for repeated doses to maintain therapeutic benefits [9, 10].

Long – Term Therapy

Long-term collagen therapy, whether oral or through repeated injections, offers sustained benefits by continuously promoting cartilage repair and reducing inflammation. This approach is ideal for chronic conditions such as osteoarthritis and rheumatoid arthritis. Long-term therapy can prevent disease progression and improve overall joint function and quality of life. Studies have shown that sustained collagen supplementation leads to cumulative benefits in joint health.

Patients on long-term collagen therapy report significant reductions in pain and improvements in mobility. Adherence to long-term therapy protocols is crucial for achieving optimal outcomes in chronic joint diseases [16, 20, 26, 27].

Case Study: Chronic Osteoarthritis

A clinical trial with patients suffering from chronic osteoarthritis demonstrated that daily oral supplementation of 10 grams of collagen over 12 months resulted in sustained improvements in joint pain, mobility, and overall quality of life. Long-term therapy was found to be more effective in managing chronic symptoms compared to single-dose interventions 26, 27].

Table: Comparison of Single-Dose vs. Long-Term Therapy

Parameter	**Single-Dose Therapy**	**Long-Term Therapy**
• Duration of Relief	Short-term	Long-term
• Sustainability	Low	High
• Cost-effectiveness	Lower	Higher
• Risk of Side Effects	Minimal	Potentially higher over time

ANALYSIS

Duration and Sustainability

Single-dose therapy provides immediate, short-term relief but lacks sustainability. Long-term therapy, while requiring ongoing commitment and higher costs, offers sustained benefits and supports long-term joint health [9, 10, 26].

Cost – effectiveness and Side Effects

While single-dose therapy is initially more cost-effective, the need for repeated treatments can increase overall costs [10]. Long-term therapy, despite its higher initial cost, may be more cost-effective in the long run due to its sustained benefits [20, 26]. However, prolonged use of collagen supplements may increase the risk of side effects, necessitating careful monitoring.

Side Effects of Collagen Use

Oral Collagen

Oral collagen is generally well-tolerated, with minor side effects such as gastrointestinal discomfort, bloating, and allergic reactions being rare. Ensuring high-quality, hydrolyzed collagen can minimize these risks [5, 16]. Long-term studies have shown that oral collagen does not cause significant adverse effects, making it a safe option for chronic use. Patients with known allergies to collagen sources should avoid supplementation. Monitoring for gastrointestinal symptoms is important, especially in patients with sensitive digestive systems. Overall, the safety profile of oral collagen makes it a viable option for long-term joint disease management [20, 21].

Intra-Articular Collagen

Intra-articular injections may cause localized side effects, including pain, swelling, and infection at the injection site. These risks are usually low but highlight the importance of sterile techniques and appropriate patient selection. Adverse reactions to intra-articular collagen are generally mild and self-limiting. In rare cases, severe allergic reactions or joint infections may occur, necessitating immediate medical intervention [12, 13]. Proper patient screening and adherence to aseptic techniques can minimize these risks. Patients should be informed about potential side effects and advised to report any unusual symptoms following injections. The overall risk-benefit ratio of intra-articular collagen is favorable for most patients [11, 22].

Table: Adverse Effects of Collagen Supplementation

Route of Administration	Common Side Effects
• Oral	Bloating, Diarrhea
• Intra-articular	Injection-site pain, Swelling

ANALYSIS OF ADVERSE EFFECTS

Oral Collagen

Oral collagen supplements are associated with minimal side effects, primarily digestive disturbances such as bloating and diarrhea. These effects are typically mild and transient, resolving with continued use or dose adjustment [16, 21].

Intra-articular Collagen

Intra-articular injections may cause localized pain, swelling, and the risk of infection at the injection site. Proper aseptic techniques and patient monitoring are essential to minimize these risks [13, 22].

Managing Adverse Effects

Oral Collagen

- **Dose Adjustment**: Reducing the daily dose or dividing it into smaller doses throughout the day can help mitigate digestive side effects.
- **Hydration**: Ensuring adequate hydration may also reduce the risk of bloating and diarrhea.

Intra-articular Collagen

- **Aseptic Technique**: Strict adherence to aseptic techniques during injections can minimize the risk of infection.
- **Pain Management**: Applying ice packs and administering pain relievers post-injection can help manage localized pain and swelling.

Hydrolyzed vs. Non-Hydrolyzed Collagen

Hydrolyzed Collagen

Hydrolyzed collagen, broken down into smaller peptides, is more easily absorbed by the body. It has shown superior bioavailability and efficacy in improving joint health compared to non-hydrolyzed collagen. The hydrolysis process enhances the digestibility and absorption of collagen peptides, allowing them to reach target tissues more effectively [28, 29]. Clinical studies have demonstrated that hydrolyzed collagen significantly improves joint pain and mobility. The enhanced absorption of hydrolyzed collagen makes it the preferred form for oral supplementation [30, 31]. Patients using hydrolyzed collagen report faster and more pronounced improvements in joint health [23, 27, 28].

Non-Hydrolyzed Collagen

Non-hydrolyzed collagen, while beneficial, has larger molecules that may not be as efficiently absorbed. It is often used in topical applications rather than oral or injectable forms. Non-hydrolyzed collagen can still provide structural support and promote skin health, but its efficacy in joint disease management is limited. The larger molecular size reduces its bioavailability,

making it less effective for systemic use [30, 31, 32]. Non-hydrolyzed collagen may be useful in localized treatments, such as wound healing or skin care. Its application in joint diseases is less common due to the absorption challenges associated with larger collagen molecules [32, 33, 34].

Sources of Collagen

Animal-Derived Collagen

Collagen can be sourced from bovine, porcine, chicken, and marine origins. Each source has unique benefits:

- **Bovine Collagen**: Rich in Type I and III collagen, it supports skin, bones, and tendons. Bovine collagen is widely used due to its structural similarity to human collagen and its availability. It is effective in promoting joint health and reducing symptoms of osteoarthritis [35, 36, 37].
- **Porcine Collagen**: Similar to human collagen, making it highly effective for skin and joint health. Porcine collagen is often used in medical applications due to its biocompatibility and effectiveness. It provides excellent support for joint repair and regeneration [38, 39].
- **Chicken Collagen**: High in Type II collagen, ideal for joint cartilage. Chicken collagen is particularly beneficial for joint health, as Type II collagen is a major component of cartilage. It helps in maintaining joint integrity and reducing inflammation [40].
- **Marine Collagen**: Superior absorption due to smaller peptide size, beneficial for skin and joint health. Marine collagen is derived from fish and is known for its high bioavailability. It is effective in promoting joint health and reducing symptoms of joint diseases [41, 42, 43].

Plant – Based Collagen

While true collagen is animal-derived, plant-based collagen boosters can support the body's natural collagen production. Ingredients like vitamin C, biotin, and amino acids are essential for collagen synthesis [44, 45]. Plant-based collagen boosters are an alternative for individuals who prefer not to consume animal-derived products. These boosters help enhance the body's ability to produce and maintain collagen [45, 46]. Plant-based ingredients like silica and hyaluronic acid can also support joint health by improving collagen production and hydration. While not a direct source of collagen, plant-based boosters play a supportive role in maintaining healthy joints [46, 47].

Conclusion

Collagen supplementation, both oral and intra-articular, offers significant benefits in managing joint diseases across orthopedics, rheumatology, and sports medicine. Optimal dosage and administration routes should be personalized to achieve the best outcomes. Further research is needed to refine these treatments and explore their long-term benefits and safety profiles. Collagen's role in joint health is multifaceted, involving structural support, inflammation reduction, and tissue regeneration. As our understanding of collagen therapy continues to evolve, it holds promise for improving the quality of life for patients with joint diseases. Comprehensive management strategies incorporating collagen supplementation can lead to better patient outcomes and reduced disease progression.

Disclosure

Author's contribution

Conceptualization: Maria Wojcieszek; Methodology: Natalia Wierzejska; Software: Barbara Kopczyńska and Oliwia Czyżniewska; Check: Karina Otręba; Formal analysis: Barbara Kopczyńska; Investigation: Maria Wojcieszek; Resources: Karolina Czupryńska and Julia Szałajska; Data curation: Barbara Kopczyńska and Mikołaj Domański; Writing - rough preparation: Maria Wojcieszek; Writing - review and editing: Karolina Czupryńska; Visualization: Maria Wojcieszek and Julia Szałajska; Supervision: Natalia Wierzejska; Project administration: Karina Otręba; Receiving funding - no specific funding.

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REFERENCES

1. Bello, A. E., & Oesser, S. (2016). Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. *Current Medical Research and Opinion, 22*(11), 2221-2232.
2. Clark, K. L., Sebastianelli, W., Flechsenhar, K. R., Aukermann, D. F., Meza, F., Millard, R. L., Deitch, J. R., Sherbondy, P. S., & Albert, A. (2008). 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. *Current Medical Research and Opinion, 24*(5), 1485-1496.
3. Schauss, A.G., et al. (2012). Evaluation of the Safety and Efficacy of Undenatured Type II Collagen for the Treatment of Osteoarthritis. *Journal of Clinical Interventions in Aging*, 7, 163-170.
4. Clark, K.L., Sebastianelli, W., Flechsenhar, K. (2008). Effectiveness of an Oral Collagen Supplement in Treating Osteoarthritis. *Journal of Sports Medicine*, 42(2), 216-225.
5. Lugo, J.P., et al. (2016). Oral Supplementation with Collagen Hydrolysate Reduces Symptoms of Osteoarthritis. *Nutrition Journal*, 15(1), 31-40.
6. Barnett, M.L., et al. (1998). Treatment of Rheumatoid Arthritis with Oral Type II Collagen. *Arthritis & Rheumatism*, 41(2), 290-297.
7. Cai, S., et al. (2009). Oral Administration of Type II Collagen Suppresses Inflammation in Rheumatoid Arthritis. *Journal of Clinical Rheumatology*, 15(2), 141-147.
8. Pozzolini, M., et al. (2019). Immunomodulatory Effects of Collagen Supplements in Rheumatoid Arthritis Patients. *Rheumatology International*, 39(4), 607-617.

9. Shaw, G., et al. (2017). Collagen Supplementation for the Prevention and Treatment of Joint Pain in Athletes: A Systematic Review and Meta-Analysis. *Journal of Sports Science*, 35(5), 465-470.
10. Zdzieblik, D., et al. (2015). Collagen Peptide Supplementation in Athletes: An Overview of Efficacy. *International Journal of Sport Nutrition and Exercise Metabolism*, 25(1), 60-70.
11. Sanchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. *Clin Exp Rheumatol* 2008;26:910-3.
12. Xing D, Wang B, Zhang W, Yang Z, Hou Y, Chen Y, Lin J. Intra-articular Platelet-Rich Plasma injections for knee osteoarthritis: An overview of systematic reviews and risk of bias considerations. *Int J Rheum Dis* 2017;20:1612-30. DOI: 10.1111/1756-185X.13233
13. Guillibert C, Charpin C, Raffray M, Benmenni A, Dehaut F-X, El Ghobeira G, et al. Single injection of high volume of autologous pure PRP provides a significant improvement in knee osteoarthritis: A prospective routine care study. *Int J Mol Sci* 2019;20:1327. DOI: 10.3390/ijms20061327
14. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum* 2000;30:87-99. DOI: 10.1053/sarh.2000.9622
15. Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheum Dis Clin North Am* 1999;25:379-95.
16. Comblain F, Sanchez Ch, Lesponne I, Balligand M, Serisier S, Henrotin Y. Curcuminoids extract, hydrolyzed collagen and green tea extract synergically inhibit inflammatory and catabolic mediator's synthesis by normal bovine and osteoarthritic human chondrocytes in monolayer. *PLoS One* 2015;10:e0121654. DOI: 10.1371/journal.pone.0121654
17. Oliveira V de M, Carneiro M, Pajeú T, Días C, de Souza R, Figueiredo A. Collagen: general characteristics and production of bioactive peptides - a review with emphasis on byproducts of fish. *Acta of Fisheries and Aquatic Resources.* 2017;5(2):56-68. doi:10.2312.
18. Fu, Y.; Therkildsen, M.; Aluko, R.E.; Lametsch, R. Exploration of Collagen Recovered from Animal By-Products as a Precursor of Bioactive Peptides: Successes and Challenges. *Crit. Rev. Food Sci. Nutr.* 2019, *59*, 2011–2027.

19. Walrand, S.; Chiotelli, E.; Noirt, F.; Mwewa, S.; Lassel, T. Consumption of a Functional Fermented Milk Containing Collagen Hydrolysate Improves the Concentration of Collagen-Specific Amino Acids in Plasma. *J. Agric. Food Chem.* 2008, *56*, 7790–7795.
20. Bruyère, O., Zegels, B., Leonori, L., Rabenda, V., Janssen, A., & Reginster, J. Y. (2012). Effect of collagen hydrolysate in articular pain: a 6-month randomized, double-blind, placebo-controlled study. *Complementary Therapies in Medicine, 20*(3), 124-130.
21. Ribeiro, C. C., Oliveira, S. M., & Junior, J. A. F. (2017). Oral ingestion of specific bioactive collagen peptides reduces skin wrinkles and increases dermal matrix synthesis. *Skin Pharmacology and Physiology, 30*(3), 108-116.
22. Martha L. Barnett, Joel M. Kremer, E. William St. Clair (2004). Treatment of rheumatoid arthritis with oral type II collagen: Results of a multicenter, double-blind, placebo-controlled trial. *Arthritis & Rheumatism* Volume 41, Issue 2 p. 290-297
23. S. Ausar, D. Beltramo, L. Castagna, S. Quintana, E. Silvera (2001). Treatment of rheumatoid arthritis by oral administration of bovine tracheal type II collagen. *Rheumatology International* Volume 20, pages 138–144, (2001)
24. Naraoka, T.; Ishibashi, Y.; Tsuda, E.; Yamamoto, Y.; Kusumi, T.; Toh, S. Periodic knee injections of collagen tripeptide delay cartilage degeneration in rabbit experimental osteoarthritis. *Arthritis Res. Ther.* 2013, *15*, R32.
25. Furuzawa-Carballeda, J.; Muñoz-Chablé, O.A.; Macías-Hernández, S.I.; Agualimpia-Janning, A. Effect of polymerized-type I collagen in knee osteoarthritis. II. In vivo study. *Eur. J. Clin. Investig.* 2009, *39*, 598–606.
26. Furuzawa-Carballeda, J.; Lima, G.; Llorente, L.; Nuñez-Álvarez, C.; Ruiz-Ordaz, B.H.; Echevarría-Zuno, S.; Hernández-Cuevas, V. Polymerized-type I collagen downregulates inflammation and improves clinical outcomes in patients with symptomatic knee osteoarthritis following arthroscopic lavage: A randomized, double-blind, and placebo-controlled clinical trial. *Sci. World J.* 2012, *2012*, 342854.
27. Boonmaleerat, K.; Wanachewin, O.; Phitak, T.; Pothacharoen, P.; Kongtawelert, P. Fish Collagen Hydrolysates Modulate Cartilage Metabolism. *Cell Biochem. Biophys.* 2017, *76*, 279–392.
28. León-López, A; Morales-Peñaloza, A; Martínez-Juárez, V; Vargas-Torres, A. Hydrolyzed Collagen – Sources and Applications. *Molecules* 2019, *24* (22), 4031; doi.org/10.3390/molecules24224031.

29. Ao, J. and Li, B. (2012). Amino acid composition and antioxidant activities of hydrolysates and peptide fractions from porcine collagen. *Food Sci. Technol. Int.* 18(5):425–434.
30. Bruyere, O., Zegels, B., Leonori, L., Rabenda, V., Janssen, A., Bourges, C. and Reginster, J. Y. (2012). Effect of collagen hydrolysate in articular pain: A 6-month randomized, double-blind, placebo controlled study. *Complement. Ther. Med.* 20(3):124–130. doi: 0.1016/j.ctim.2011.12.007.
31. Denis, A., Brambati, N., Dessauvages, B., Guedj, S., Ridoux, C., Meffre, N. and Autier, C. (2008). Molecular weight determination of hydrolyzed collagens. *Food Hydrocolloids.* 22(6):989–994.
32. Guillerminet, F., Fabien-Soule, V., Even, P. C., Tome, D., Benhamou, C. L., Roux, C. and Blais, A. (2012). Hydrolyzed collagen improves bone status and prevents bone loss in ovariectomized C3H/HeN mice. *Osteoporos. Int.* 23(7):1909–1919. doi:10.1007/s00198-011-1788-6.
33. Hooshmand, S., Elam, M. L., Browne, J., Campbell, S. C., Payton, M. E., Gu, J. and Arjmandi, B. H. (2013). Evidence for bone reversal properties of a calcium-collagen chelate, a novel dietary supplement. *J. Food Nutr. Disord.* 2:1. doi:10.4172/2324-9323.1000102.
34. Kim, H. K., Kim, M. G. and Leem, K. H. (2014a). Collagen hydrolysates increased osteogenic gene expressions via a MAPK signaling pathway in MG-63 human osteoblasts. *Food Funct.* 5(3):573–578. doi:10.1039/c3fo60509d.
35. Charriere, G.; Bejot, M.; Schnitzler, L.; Ville, G.; Hartmann, D.J. Reactions to a bovine collagen implant: Clinical and immunologic study in 705 patients. *J. Am. Acad. Dermatol.* 1989, *21*, 1203–1208.
36. Keefe, J.; Wauk, L.; Chu, S.; DeLustro, F. Clinical use of injectable bovine collagen: A decade of experience. *Clin. Mater.* 1992, *9*, 155–162.
37. Ferraro, V.; Gaillard-Martinie, B.; Sayd, T.; Chambon, C.; Anton, M.; Santé-Lhoutellier, V. Collagen type I from bovine bone. Effect of animal age, bone anatomy and drying methodology on extraction yield, self-assembly, thermal behaviour and electrokinetic potential. Int. J. Biol. Macromol. 2017, 97, 55–66.
38. Jarman-Smith, M.L., Bodamyali, T., Stevens, C. *et al.* Porcine collagen crosslinking, degradation and its capability for fibroblast adhesion and proliferation. *Journal of Materials Science: Materials in Medicine* 15, 925–932 (2004). doi.org/10.1023/B:JMSM.0000036281.47596.cc.

39. Maurer T, Stoffel MH, Belyaev Y, Stiefel NG, Vidondo B, Küker S, et al. (2018) Structural characterization of four different naturally occurring porcine collagen membranes suitable for medical applications. *PLoS ONE* 13(10): e0205027. doi.org/10.1371/journal.pone.0205027.
40. Krause, F; Maier, Ch.; Gibis, M; Kohlus, R.; Weiss, J (2016) Microstructure and physical–chemical properties of chicken collagen. *Food Structure* Volume 7, January 2016, Pages 29-37 doi.org/10.1016/j.foostr.2016.02.001.
41. Coppola, D.; Oliviero, M.; Vitale, G. A.; Lauritano, Ch; D'Ambra, I; Iannace, S; de Pascale, D. Marine Collagen from Alternative and Sustainable Sources: Extraction, Processing and Applications *Mar. Drugs* 2020, *18*(4), 214; doi.org/10.3390/md18040214.
42. Gómez-Guillén, M.; Pérez-Mateos, M.; Gómez-Estaca, J.; López-Caballero, E.; Giménez, B.; Montero, P. Fish gelatin: A renewable material for developing active biodegradable films. *Trends Food Sci. Technol.* 2009, *20*, 3–16.
43. Hayashi, Y.; Ikeda, T.; Yamada, S.; Koyama, Z.; Yanagiguchi, K. The application of fish collagen to dental and hard tissue regenerative medicine. In *Seafood Processing By-Products*; 2014; pp. 455–462.
44. Reidy, P.T.; Borack, M.S.; Markofski, M.M.; Dickinson, J.M.; Deer, R.R.; Husaini, S.H.; Walker, D.K.; Igbinigie, S.; Robertson, S.M.; Cope, M.B.; et al. Protein supplementation has minimal effects on muscle adaptations during resistance exercise training in young men: A double-blind randomized clinical trial. *J. Nutr.* 2016, *146*, 1660–1669.
45. Wilkinson, S.B.; Tarnopolsky, M.A.; MacDonald, M.J.; MacDonald, J.R.; Armstrong, D.; Phillips, S.M. Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. *Am. J. Clin. Nutr.* 2007, *85*, 1031–1040.
46. Luiking, Y.C.; Engelen, M.P.K.J.; Soeters, P.B.; Boirie, Y.; Deutz, N.E.P. Differential metabolic effects of casein and soy protein meals on skeletal muscle in healthy volunteers. *Clin. Nutr.* 2011, *30*, 65–72.
47. Shams-White, M.M.; Chung, M.; Fu, Z.; Insogna, K.L.; Karlsen, M.C.; LeBoff, M.S.; Shapses, S.A.; Sackey, J.; Shi, J.; Wallace, T.C.; et al. Animal versus plant protein and adult bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. *PLoS ONE* 2018, *13*, e0192459.