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Understanding Collagen Supplements in Arthritis – Immunomodulation with Undenatured Collagen II Versus Cartilage Building with Hydrolysed Collagen II

Varsha Narayanan[1]*, Rajesh Gandhi[2]

[1]Health and Pharmaceutical Consultant, Dr Varsha's Health Solutions, Andheri west, Mumbai, India.

[2]Orthopedic Surgeon, Gandhi Nursing Home, Andheri West, Mumbai, India.

drvarsha@rediffmail.com

***Corresponding Author:** Varsha Narayanan, Health and Pharmaceutical Consultant, Dr Varsha's Health Solutions, Andheri west, Mumbai, India.*

Abstract

Rheumatoid Arthritis is known to have a T cell mediated autoimmune aetiology causing joint cartilage destruction. Osteoarthritis, though regarded as a degenerative disease, also shows a T cell immune response and inflammatory cartilage damage. Both types of Arthritis at a cellular level show T helper cell activation, involvement of pro-inflammatory cytokines and increased destruction of cartilage by Matrix Metalloproteinase enzymes. There is also evidence of relative suppression of anti-inflammatory cytokines and T regulatory cells which can perpetuate the cartilage loss. Supplementing hydrolysed Collagen type II to aid the body rebuild joint cartilage in the scenario of continuous cartilage destruction may not give the desired results. Therefore, reduction of inflammatory cartilage damage through the mechanism of specific immunomodulation by preventing immune response against collagen type II in joint cartilage, appears to be a scientifically rational option in both Rheumatoid Arthritis and Osteoarthritis.

Keywords: *Rheumatoid Arthritis, Osteoarthritis, Cartilage, Undenatured Collagen Type II, T cell, autoimmune, immunomodulation, Matrix Metalloproteinase, Cytokines.*

Introduction

Rheumatoid Arthritis (RA) is an inflammatory condition comprising of cartilage destruction and joint inflammation caused by an autoimmune T cell mediated process. It leads to inflammation of the joint space with initial swelling and pain followed by stiffness and increasing loss of joint movement. It maybe associated with systemic symptoms like fever, night sweats, fatigue, malaise, and gastro intestinal (GI) symptoms due to associated other autoimmune diseases like systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, vasculitis and inflammatory bowel disease (IBD).[1]

Osteoarthritis (OA) is considered to be a degenerative disease caused by long term and repeated wear and tear of the cartilage of weight bearing joints leading to loss of cartilage followed by exposure and damage to underlying bone surfaces.[2]

RA usually occurs at a younger age with a rapid onset, presenting as a symmetrical polyarthritis involving the smaller joints of hands and feet. OA has a gradual onset and is a disease seen more after 60 years of age. Involvement is asymmetric in OA and usually of the large weight bearing joints like knee and hip. The morning stiffness characteristic of Arthritis lasts much longer (>45 min) in RA as compared to OA.[3]

The joint hyaline cartilage is made up of chondrocytes which synthesize and maintain the main components of cartilage: Type II Collagen and Extracellular Matrix (ECM) Proteoglycans containing Glycosaminoglycans (GAGs) like Chondroitin sulphate and Hyaluronic acid.[4] Chondrocytes also produce lubricating proteins like Lubricin in the synovial fluid and surface. More the loss and destruction of cartilage lesser the number of chondrocytes and thereby lesser the synthesis of Cartilage components - Collagen type II and GAGs.

This leads to an overall imbalance between excess and ongoing cartilage loss, and inadequate cartilage synthesis.[5]

Immune Mediated Inflammation in Rheumatoid Arthritis and Osteo-arthritis

Rheumatoid Arthritis is postulated to be due to recognition by T helper cells of certain cartilage joint proteins acting as antigens. The activated T helper (CD4) cells then act by increasing pro-inflammatory cytokines like IL1, IL6 and TNF-A and further stimulate B cells to produce Auto-antibodies. One of the antigens studied is Citrullinated Collagen Type II against which autoantibodies have been seen in more than 70% RA patients called Anticitrullinated Protein Peptide Autoantibodies (ACPA).[6] Citrullinated antigens have been correspondingly extracted from the synovial fluid of these RA patients. Further immune complexes of Rheumatoid factor (RF: antibodies to Fc of ACPA) with antigen-ACPA mediate complement activation and joint cartilage collagen damage. Such antibodies and their complexes have also been found in other autoimmune diseases. Smoking, genetic, and environmental factors characterizes risks in this phenotype with associated late occurrence of signs and symptoms of inflammation. The other type of antigen in RA patients is fibrillar Collagen type II (CII) restricted to hyaline cartilage, and seen in up to 27% RA patients especially around the time of RA diagnosis (early inflammation phenotype).[7] Anti-CII-CII immune complexes (IC) can induce pro-inflammatory cytokines and chemokines from macrophages and neutrophils.

Recent concepts in Osteoarthritis have shown that inflammation in the joint as a result of T cell mediated immune response plays an important role in ongoing cartilage destruction as well as symptoms of pain, swelling and loss of mobility. Studies have shown increased number of CD4 cells in the serum and synovial fluid of OA patients as a response to increased collagen wear and tear protein debris.[8] T cells in the synovial fluid of OA patients expressed class II HLA (an indicator of activated T cells) and the percentages of CD4+ and CD8+ cells in the synovial fluid of OA patients were even found to be similar to those found in RA patients.[9] T cells recognize glycosylation alterations in damaged collagen II in joint cartilage, and are thereby activated leading to increase in pro-inflammatory cytokines like IL1, IL6, and TNF alpha, which activate matrix metalloproteinase (MMP) causing further inflammatory destruction of cartilage.[10,11] Consequently, there is a decrease in the action of T regulatory cell action and anti-inflammatory cytokines (IL10 and TGF beta) which have a suppressive effect on MMPs.[12,13]

Cartilage destruction leads to release of phospholipids converted to arachidonic acid by phospholipases which are then converted by Cyclo-oxygenase (COX2) and Lipo-oxygenase (5LOX) to prostaglandins and leukotrienes respectively. The inflammatory actions of prostaglandins (PGE2) in causing pain, swelling and increase in temperature are well studied. Therefore Non-Steroidal Anti-inflammatory Drugs (NSAIDs-COX inhibitors) are the most recognized drugs for symptomatic relief in Arthritis management, but they do not affect the immune mechanism of cartilage destruction.[14] Leukotrienes also mediate cartilage destruction by increasing pro-inflammatory cytokines, like interleukin (IL)-1 and Tumour necrosis factor (TNF)-αwhich activate MMP mediated cartilage destruction, activate Interstitial Cell Adhesion Molecules (ICAMs) and chemotactic attraction of inflammatory cells (phagocytes releasing Reactive Oxygen Species: ROS) [15-16]

Therefore, preventing and reducing T cell mediated immune response to type II collagen which leads to inflammatory cartilage damage in both forms of Arthritis can serve as the central pathway to long term clinical management complementing short term and periodic symptomatic treatment with NSAIDs.

Undenatured (Native) Collagen Type II

The joint cartilage is made up predominantly of type II collagen synthesized by chondrocytes. Collagen is a complex protein present only in animals and humans, with a triple helical structure.

Undenatured Collagen Type II is non-hydrolysed collagen with intact structure, active epitopes and antigenicity, which is lost in hydrolysed collagen.[17,18] Undenatured type II collagen is extracted from chicken sternum using little or no heat (unlike the high heat used in hydrolysed collagen), and very limited processing just enough to concentrate the collagen and make it soluble.[27] The manufacturing process ensures that the collagen remains biologically active in its most native, triple helix form with antigenic sites (epitopes) intact for immunomodulation. ELISA

studies with simulated human gastric fluid at 32 degrees C and pH 2 have shown maintenance of triple helical form of Undenatured Type II Collagen.[17]

Our body cannot absorb intact collagen therefore Collagen supplements are made up of heat denatured and acid hydrolysed collagen peptides with the prospect of easier absorption by the gut and thereafter assimilation into the triple helical collagen type II by the joint cartilage chondrocytes.[19] However, the use of hydrolysed collagen supplements would be rational and effective only if on-going immune mediated inflammatory destruction of cartilage can be arrested.

The mechanism of action of Undenatured Collagen Type II (Figure 1) is not related to its absorption or assimilation as it acts in the small intestine itself through a process called oral tolerance (Figure 2) to help slow down the T cell mediated inflammatory damage of type II collagen in the joint cartilage.[17] Payer's patches (also called (GALT- Gut-associated lymphoid tissue) are GI lymph nodes rich in T cells. Repeated and low dose administration of Undenatured Collagen II make Dendritic cells (DCs) in GALT take it up in its glycosylated form. This makes T helper cells recognize the antigen epitopes, inducing an initial mild immune response and then gradually developing 'tolerance' thereby attenuating the immune response against cartilage collagen II. This stimulates T regulatory cell and suppresses T helper cell stimulation and response thereby increasing anti-inflammatory cytokines like IL 10 and TGF Beta which suppresses the cartilage collagen degrading MMP enzymes.[20,21]Therefore,endogenous collagen synthesis, or collagen peptide supplementation can be more effective once inflammatory cartilage collagen destruction issuppressed.

The difference between undenatured and hydrolysed collagen supplements lies clearly in the former reducing cartilage destruction while the latter intending to help regenerate and rebuild cartilage (table 1). Focussing on rebuilding cartilage without arresting ongoing inflammatory damage would be a less effective and rational treatment approach.

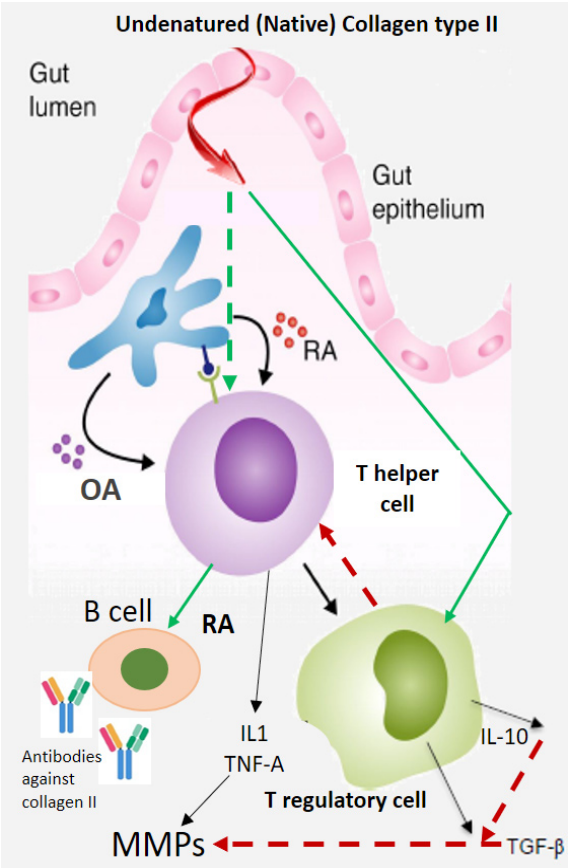

Fig 1. *Mechanism of Action of Undenatured (Native) Collagen Type II.*

Table 1. *Difference between Undenatured and Hydrolysed Collagen Type II*

	Undenatured or Native Collagen Type II	Hydrolysed Collagen (Collagen Hydrolysates)
1	Extraction, concentration and solubilization done with little or no heat, and limited processing	Heat denatured and acid hydrolysed into collagen peptides
2	Not absorbed by the intestine – acts in the intestine itself on gut associated lymphoid tissue (GALT or Payer's patches)	Absorbed by the intestine to be taken up by chondrocytes in joint cartilage
3	Intact antigenic sites and native structure	Antigenic sites and native structure is lost
4	Acts through 'oral tolerance' by reducing T cell immune response to type II collagen there by reducing inflammatory cartilage damage	Acts through assimilation by chondrocytes to synthesize collagen type II along with ECM components and thereby rebuild damaged joint cartilage.
5	Oral intake is in small doses (40mg capsule containing 10mg Collagen with 1.2mg active Undenatured Collage II) once daily.	Oral intake is in large doses (5-10g/day), as capsules/ powders, commonly in combination with ECM-GAG components like glucosamine, chondroitin sulphate and hyaluronic acid.

Efficacy and Safety of Undenatured Collagen Type II in RA

The efficacy and tolerance of Undenatured Collagen type II has been demonstrated in Rheumatoid Arthritis.

In an early phase 2 study, 274 patients with active RA were randomized to receive placebo or 1 of 4 dosages (20, 100, 500, or 2,500 mcg/day) of oral undenatured chicken collagen type II(CCII) for 24 weeks.[22] Positive effects were observed with the lowest dosage tested, and the presence of serum antibodies to type II collagen at baseline predicted better response to therapy. In the 20 mcg/day treatment group, there was a statistically significant improvement versus placebo in the percentage of patients who met the cumulative Paulus criteria during the study (39% vs 19%). No side effects were associated.

*Later two separate studies*assessed the efficacy and safety of CCII (100mcg/day) in rheumatoid arthritis (RA) compared with methotrexate (MTX 10mg/week) in 24-week double blind designs with 236 and 503 patients respectively. In the both studies, there was a statistical decrease in pain, morning stiffness, tender joint count, swollen joint count, Health Assessment Questionnaire score, and investigator and patient assessment of function in both groups. In the first study, at 24 weeks, 68.57% of patients in the Collagen type II group and 83.02% in the MTX group met the American College of Rheumatology 20% improvement criteria (ACR20), and 40.95% and 57.54%, respectively, met the ACR50 criteria.[23] In the second phase 3 study at 24weeks, 41.55% of patients in the CCII group and 57.86% in theMTX group met the American College of Rheumatology 20%improvement criteria (ACR-20) and 16.89% and 30.82%,respectively, met the ACR 50% improvement criteria (ACR-50).[24] The ACR20 and ACR50 response rates in the CCII group were lower than those in the MTX group, however adverse effects (mainly gastro-intestinal) were significantly fewer and milder in the CCII group ($P < 0.05$). RF reduced in both groups but reduction did not reach significance. ESR and CRP was seen to reduce only in MTX group.

Efficacy and Safety of Undenatured Collagen Type II in OA

The efficacy and tolerance of Undenatured Collagen Type II – Undenatured Collagen II (1.2mg) in Osteo-arthritis has been demonstrated in various clinical studies.

In the first study versus combination of Glucosamine and Chondroitin sulphate (G+C: 1500+1200 mg/ day), Undenatured Collagen II (UCII) treatment was more efficaciousresulting in a significant reduction in all assessments from the baseline, at 90 days which was not observed in G+C treatment group(N=26/ group). Treatmentwith UC II reduced the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC score), Visual Analog Scale (VAS) score and Lequesne's Functional index (LFI) scoreby 33%, 40%, 20% as compared to 14%, 15.4% and 6% in G+C treated group after 90 days suggesting a more significant reduction in pain and enhancement in daily activities and quality of life.[25] A higher number of subjects (23%) on G+C demonstrated adverse events possibly related to product as compared to 11.4%

of subjects on UC II (P<0.05). For UC II the possible adverse events related to products were intermittent constipation and headaches while for G+C it was bloating, stomach pain, rash, swelling around the eyes and scars, hives and headache.

In the second study 191 volunteers were randomized into three groups receiving a daily dose of UC II (40 mg capsule containing 1.2mg active undenatured collagen II), G+C (1500 mg G+1200 mg C), or placebo. At day 180, the UC II group demonstrated a significant reduction in overall WOMAC score compared to placebo and G+C: UC II compared to placebo (−551 vs. −414; 95 % CI −232 to −42; p = 0.002) and compared to G+C (−551 vs. −454; 95 % CI −190 to −3; p = 0.04). Supplementation with UC II also resulted in significant changes for pain and stiffness WOMAC subscales versus G+C and placebo: pain (24 vs 19.2 vs 17; p = 0.016 vs. G+C; p = 0.0003 vs. placebo;); stiffness (23.8 vs 19.4 vs 17.8; p=0.044 vs. G+C ; p = 0.004 vs. placebo); and significant changes for physical function versus placebo (22.5 vs 17.3;p = 0.007 vs. placebo). The UC II supplemented group had a significant decrease in mean VAS score at day 180 versus both G+C and placebo(22.6 vs 18.4 vs 17.0; p = 0.025 vs G+C; p = 0.002 vs placebo). A significant reduction was also observed in the LFI score forthe UC II group at day 180 versus G+C and placebo (2.9 vs 2.2 vs 2.1; p = 0.008 vs G+C; p = 0.009; vs placebo). No significant change was observed between the G+C and placebo for both VAS and LFI scores. Safety outcomes did not differamong the groups. UC II improved knee joint symptoms in knee OA subjects and was well-tolerated.[26] 15 product related adverse events were seen, 14 of which belonged to the GC group (gastro-intestinal) and 1 to placebo while no AEs noted for the UC II cohort were deemed to be product related.

Another study in 39 patients was performed to evaluate the effect of adding Undenatured Native Collagen Type II to Acetaminophen (Paracetamol) 1500mg/day.[27]After 3 months of treatment, the patients of the combination group showed significant improvements in VAS walking (p<0.001), WOMAC pain (p=0.003), WOMAC total (p=0.004), WOMAC physical functioning (p=0.016) scores and subscales of SF36 bodily pain score (p=0.016) while the same was not significant with the group receiving only Acetaminophen. Comparisons between the groups revealed a significant difference in VAS walking score in favour of the combination group (50% reduction) as compared to the Acetaminophen monotherapy group (p=0.002).

A study done in non-arthritic healthy volunteers who had knee pain on physical activity showed significantly better response to Undenatured Collagen Type II versus placebo in increasing degree of knee extension and time to pain onset on physical activity.[21]

A non-interventional, real-life study to determine safety and efficacy of Undenatured Collagen type II in Indian population was done in 226 patients across 18 Orthopaedic doctors in India.[28] There was significant reduction in WOMAC score and VAS score, with a mean change of -20.7±12.6 (p<0.0001) and -3.3±1.8 (p<0.0001) respectively from baseline to day 90 with the use of Undenatured collagen II. A low AE rate of 4.5% (mainly gastrointestinal disturbance and headache) was seen.

Collagen Hydrolysates

Collagen supplements in the form of Hydrolysed Collagen (Collagen Hydrolysate) are also available in the market often in combination with ECM-GAG substances like Glucosamine, Chondroitin Sulphate and Hyaluronic acid, and sometimes with added Vitamins and Minerals. Collagen II is present in large doses in such formulations to be absorbed effectively to rebuild cartilage. According to published research, orally administered collagen hydrolysate formulations have been shown to be absorbed intestinally, to accumulate in cartilage, and stimulate a statistically significant increase in synthesis of extracellular matrix macromolecules by chondrocytes (p < 0.05 compared with untreated controls).[29] These findings suggest mechanisms that might help patients affected by joint disorders such as OA, however evidence in RA is currently non-conclusive. Four open-label and three double-blind studies were identified and reviewed, and although many of these studies did not provide statistical significance of improvement in inflammatory and symptomatic Arthritic parameters, the findings showed collagen hydrolysate to be safe and to provide improvement in some measures of pain and function in OA and other arthritic conditions.

In a double-blind, placebo-controlled, randomised trial with collagen peptides isolated from pork skin (PCP) and bovine bone (BCP) the effectiveness of orally supplemented collagen peptide to control the progression of osteoarthritis in patients diagnosed

with knee osteoarthritis was studied.[30] There was significant reduction from baseline to week 13 in the primary end points of WOMAC and VAS scores and in the secondary end point of QOL (Quality of Life) score in subjects of both PCP and BCP groups, while in subjects with placebo group these end point indices remained unchanged. ($P < 0.01$)

Conclusion

It is evident that T cell immune mediated response against collagen type II is one of the key pathological mechanisms of continuous inflammatory cartilage damage in both Osteoarthritis and Rheumatoid Arthritis. Currently collagen supplements are available in the market in the form of both Undenatured Collagen type II, and Collagen II Hydrolysate (peptides). Very often the two are confused to be similar by the patients purchasing it on their own. It is important to therefore educate Arthritis patients about the difference and clinical relevance of both kinds of collagen supplements. One can consider initiating treatment with analgesic-anti-inflammatory medicines like NSAIDs to provide immediate symptomatic relief, along with Undenatured Collagen type II supplements to work on immune modulation and reduction in inflammatory cartilage damage.

There after a trial of gradually withdrawing NSAIDs over a few weeks and continuation of Undenatured Collage II for 3 months can be made. Subsequently hydrolysed Collagen II and ECM-GAG supplements to build joint cartilage along can be introduced with the Undenatured collagen supplements, which can be withdrawn over next 3 months.. This can contribute to a more scientifically rational approach to the three cornerstones of Arthritis management: Symptomatic relief, reducing inflammatory cartilage damage, and improving cartilage building. Future randomized clinical studies are suggested combining such approaches in Arthritis management to study its effect on improving quality of life in Arthritis patients.

References

[1] Simon TA, Kawabata H, Ray N,Baheti A, Suissa S, Esdaile JM. Prevalence of Coexisting Autoimmune Disease in Rheumatoid Arthritis: A Cross-Sectional Study AdvTher (2017) 34:2481–2490

[2] Haq I, Murphy E, Dacre J. Osteoarthritis- Review. Postgrad Med J 2003;79:377–383

[3] Manek NJ, Lane NE. Osteoarthritis: Current Concepts in Diagnosis and Management. *Am Fam Physician.* 2000 Mar 15;61(6):1795-1804.

[4] Goldring MB. Chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism in health and osteoarthritis. TherAdvMusculoskelet Dis. 2012 Aug; 4(4): 269–285

[5] Maldonado M, Nam J. The Role of Changes in Extracellular Matrix of Cartilage in the Presence of Inflammation on the Pathology of Osteoarthritis. Biomed Res Int. 2013; 2013: 284873.

[6] Yoshida M, Tsuji M · Kurosaka D, Kurosaka D, Yasuda J, Ito Yet al.Autoimmunity to citrullinated type II collagen in rheumatoid arthritis. Mod Rheumatol (2006) 16:276–281

[7] Manivel VA, Mullazehi M, Padyukov L, Westerlind H, Klareskog L, Alfredsson L et al. Anticollagen type II antibodies are associated with an acute onset rheumatoid arthritis phenotype and prognosticate lower degree of inflammation during 5 year follow-up. Ann Rheum Dis 2017;**76**(15): 29–1536

[8] Li Y-s, Luo W, Zhu S-a and Lei GH. T Cells in Osteoarthritis: Alterations and Beyond. Front. Immunol 2017. 8:356.

[9] Hussein MR, Fathi NA, El-Din AM, Hassan HI, Abdullah F, Al-Hakeem E, et al. Alterations of the CD4(+), CD8 (+) T cell subsets, interleukins-1beta, IL-10, IL-17, tumor necrosis factor-alpha and soluble intercellular adhesion molecule-1 in rheumatoid arthritis and osteoarthritis: preliminary observations. PatholOncol Res (2008) 14(3):321–8. doi:10.1007/s12253-008-9016-1

[10] Zhang JM, An J (2007). "Cytokines, inflammation, and pain". International Anesthesiology Clinics. 45 (2): 27–37.

[11] Wassilew GI, Lehnigk U, Duda GN, Taylor WR, Matziolis G, Dynbil C. The Expression of Proinflammatory Cytokines and Matrix Metalloproteinases in the Synovial Membranes of Patients with Osteoarthritis Compared with Traumatic Knee Disorders. Arthroscopy: The Journal of Arthroscopic & Related Surgery. Volume 26, Issue 8, August 2010, 1096-1104

[12] Carter NA, Rosser EC, Mauri C. Interleukin-10 produced by B cells is crucial for the suppression of Th17/Th1 responses, induction of T regulatory type 1 cells and reduction of collagen-induced arthritis. Arthritis Research & Therapy 2012,14:R3.

[13] Wan YY, Flavell RA.TGF-Beta and Regulatory T Cells. Regulatory T Cells and Clinical Application pp 91-109.

[14] Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. ArteriosclerThrombVasc Biol. 2011 May; 31(5): 986–1000.

[15] Martel-Pelletier J, Mineau F, Fahmi H, Laufer S, Reboul P, Boileau C, et al. Regulation of the expression of 5-lipoxygenase-activating protein/5-lipoxygenase and the synthesis of leukotriene B(4) in osteoarthritic chondrocytes: role of transforming growth factor beta and eicosanoids. Arthritis Rheum 2004;50:3925-33.

[16] He W, Pelletier JP, Martel-Pelletier J, Laufer S, Di Battista JA. Synthesis of interleukin 1beta, tumor necrosis factor-alpha, and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with anti-inflammatory cytokines. J Rheumatol2002;29:546-53.

[17] Bagchi D, Misner B, Bagchi M, Kothari SC, Downs BW, Fafard RD, Preuss HG. Effects of Orally Administered Undenatured Type II Collagen against Arthritic Inflammatory Diseases: A mechanistic exploration. Int J Clin Pharm Res 2002: XXII (3/4). 101-110.

[18] Trentham DE, Halpner AE, Trentham RA, Bagchi M, Kothari S, Preuss HG et al. Use of Undenatured Type II Collagen in the treatment of Rheumatoid Arthritis. Clinical Practice of Alternative Medicine 2001;2(4):254-59.

[19] Abraham. Collagen for Joint Health. Supplements in Review. Feb 19, 2017.

[20] Park KS., Park MJ., Cho, ML, Kwok SK, Ju JH, Jae-Ko H, et al. Type II collagen oral tolerance; mechanism and role in collagen-induced arthritis and rheumatoid arthritis Mod Rheumatol 2009; 19: 581.

[21] Lugo PJ, Saiyed ZM, Lau, FC, Molina JPL, Pakdaman M, Shami AN et al. Undenatured type II collagen for joint support: a randomized, double-blind, placebo-controlled study in healthy volunteers. J IntSoc Sports Nutr. 2013; 10: 48.

[22] Barnett ML, Kremer JM, Claire EW, Clegg DO, Furst D, Weisman M et al. Treatment of Rheumatoid Arthritis with Oral type II collagen. Arthritis and Rheumatism 1998; 41(2): 290-297.

[23] Zhang LL, Wei W, Xiao F, Xu JH, Bao CD, Ni LQ et al. A Randomized, Double-Blind, Multicenter, Controlled Clinical Trial of Chicken Type II Collagen in Patients With Rheumatoid Arthritis. Arthritis & Rheumatism (Arthritis Care & Research) Vol. 59, No. 7, July 15, 2008, pp 905–910.

[24] Wei W, Zhang LL, Xu JH, Xiao F, Bao CD, Ni LQ et al A multicenter, double-blind, randomized, controlled phase III. clinical trial of chicken type II collagen in rheumatoid arthritis. *Arthritis Research & Therapy* 2009, 11:R180

[25] Crowley DC, Lau FC, Sharma P, Evans M, Guthrie N, Bagchi M et al.Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. *International Journal of Medical Sciences* 2009; 6(6):312-321

[26] Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind,placebo-controlled study. Nutrition Journal (2016) 15:14

[27] Bakilan F, Armagan O, Ozgen M, Tascioglu F, Bolluk O, OzkanAlatas O. Effects of Native Type II Collagen Treatment on Knee. Osteoarthritis: A Randomized Controlled Trial. Eurasian J Med 2016; 48: 95-101

[28] Mehra A, Anand P, Borate M, Pal P, Kamble S, Mehta KD et al. A non-interventional, prospective, multicentric real life Indian study to assess safety and effectiveness of un-denatured type 2 collagen in management of osteoarthritis. Int J Res Orthop. 2019 Mar;5(2):315-320

[29] Bello AE, Oesser S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. Curr Med Res Opin. 2006 Nov;22(11):2221-32.

[30] Kumar S, Sugihara F, Suzuki K, Inoue N, Vekateshwarathirukumara S. A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis.J Sci Food Agric. 2015 Mar 15;95(4):702-7

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