Finding a point of difference in the evolving collagen supplements market

Abstract

Recent insights reveal that the collagen market is expanding, creating exciting opportunities for dietary supplement manufacturers to innovate in the joint health sector. However, staying competitive in this evolving arena is challenging, especially when looking to develop novel solutions with widely researched ingredients that are also easy to formulate. This whitepaper discusses evidence that native (undenatured) type II collagen is effective in supporting joint health at lower doses, therefore meeting increasing consumer demand for convenient products that support their health.

Joint health & mobility: An evolving market

Joint health is now an important public health concern across the globe, largely due to the ageing population. Age can significantly impact our muscles, bones and joints; 45% of individuals aged 65+ say they experience joint pain, which affects their overall mobility and independence.[1] Furthermore, staying fit and active as we age are increasingly important health focuses – especially for senior consumers who are taking a more proactive approach to supporting their joint health. However, consumers of all ages can be affected by joint discomfort. Several reports, for instance, demonstrate that sporty people, the 40+ population and women experiencing menopause commonly experience joint discomfort or mobility issues.[2,3,4] These trends have given significant momentum to the joint health sector and are a major driving force in the emergence of innovative joint health solutions. Between 2019 – 2024 alone, it is forecast that the global bone and joint ingredients market will grow at a CAGR of 6.3% to meet this demand.[5]

Collagen: Driving growth in the joint health category

As well as the ageing population and trend towards staying active and healthier for longer, ingredients are also driving growth in the joint health segment. Glucosamine and chondroitin have long been used as active ingredients for joint health. However, other innovative ingredients, such as collagen, are now gaining rapid market share as a result of rising consumer awareness, driving significant growth in the category. According to recent market data, in 2020 alone, collagen dietary supplement sales grew by 38% in the USA.[6] As a result, the joint health category is seeing its best overall growth since 2008.

Type II collagen: The main structural protein in cartilage

Collagen is the main component of connective tissues that make up tendons, ligaments, skin and cartilage. Although it has many important functions in the body, collagen is best known for its structural role – providing a structural framework for tissues throughout the body.[7] Of the 28 different types of collagen that have been identified, type II collagen is the main structural protein in cartilage. Both native (undenatured) type II collagen and hydrolysed (denatured) collagen are available for commercial use in joint health products. However, there are significant differences between the two forms.

Did you know?

Native type II collagen and undenatured type II collagen are the same molecule, but known by different terms throughout the joint health category.

Native type II collagen – also known as undenatured or non-hydrolysed type II collagen throughout the nutrition industry – is collagen in its biologically active form.

Hydrolysed collagen – or denatured collagen – is collagen that has been broken down into smaller peptide molecules.

Figure 1: The triple helix structure of native (undenatured) type II collagen

Native type II collagen vs. hydrolysed collagen: What's the difference?

In its natural form, collagen has a folded triple helix structure consisting of long polypeptide chains (see figure 1). Hydrolysed collagen is manufactured via a specific hydrolysis process, where enzymes "cut" the triple helix molecule into smaller pieces, i.e. short-chain peptides. This is why hydrolysed collagen is also known as collagen peptides, or denatured type II collagen.

Native type II collagen on the other hand, is not hydrolysed and maintains its characteristic three-dimensional structure.

Different mechanisms of action

The mechanism by which each collagen acts differs. Native (undenatured) type II collagen works via an immune-mediated process, known as oral tolerance. Through this mode of action native type II collagen is recognised by the immune system as a known substance and deactivates the body's immune response against its own collagen. Alternatively, hydrolysed collagen peptides are highly bioavailable, resulting in a source of the specific amino acids for *de novo* synthesis of collagen. As such, hydrolysed collagen peptides act as building blocks to maintain and rebuild cartilage.

Effectiveness at lower doses

The daily dose and intake required for both collagens to be effective in the body varies greatly. The native (undenatured) type II collagen form is recommended at doses as low as 40 mg/day. Meanwhile, the recommendation for hydrolysed collagen is 10 g/day (see figure 2). The low dosage required for native type II collagen therefore mirrors consumer demand for easy-to-consume, convenient products, offering an innovative alternative to supplement manufacturers.

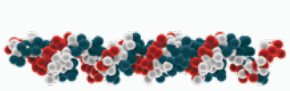
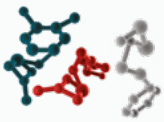
	NATIVE TYPE II COLLAGEN	HYDROLYSED COLLAGEN
MOLECULE	Native (undenatured) form - triple helix 	Denatured - cut into small peptides 
TYPES OF COLLAGEN	Type II (specific)	Non (specific)
ABSORPTION	No	Yes
MECHANISM OF ACTION	Immune mediated	Anabolic
MAIN EFFECT	Decrease of collagen destruction	Increase of collagen production
DOSE	40 mg	10 g

Figure 2: Native type II collagen vs. hydrolysed collagen

The role of the immune system in joint health

Joint disorders involving inflammation and cartilage erosion, such as arthritic diseases, are characterised by an autoimmune component in which the immune system acts against the body's own type II collagen.[8] Classically, osteoarthritis (OA) has been characterised as a degenerative, wear-and-tear disease. However, recent scientific research has identified it as an immunopathological disease – in other words, a disease in which the immune system plays a key role.

That is because in OA, products from collagen breakdown can be recognised by immune cells as potentially harmful. As a consequence, an immune response against collagen is activated, leading to inflammation and cartilage degradation, further damaging the joints.

Cartilage degradation & immune response

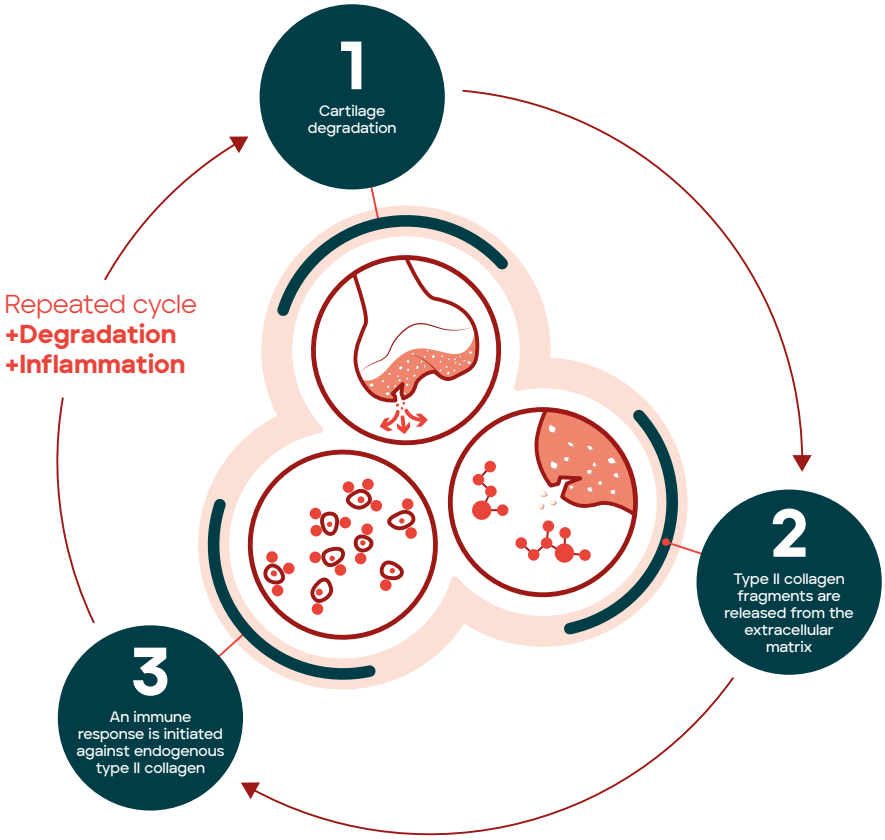


Figure 3: Autoimmune response to collagen breakdown

Oral tolerance: An immune-mediated response

Studies show that supplementing native (undenatured) type II collagen can help modulate the immune response against endogenous type II collagen, thus supporting joint health.[9]

Thanks to this specific mechanism of action, it takes just a small amount of native type II collagen to support joint health. This is why the standard dose of ingredients containing native collagen is just 40 mg, once daily, whereas dosages for hydrolysed collagen can be up to 10 g/day.

The positive immune modulation promoted by native collagen intake – its ability to prevent the immune response against type II collagen produced by the body – has been receiving increasing interest across the scientific community.

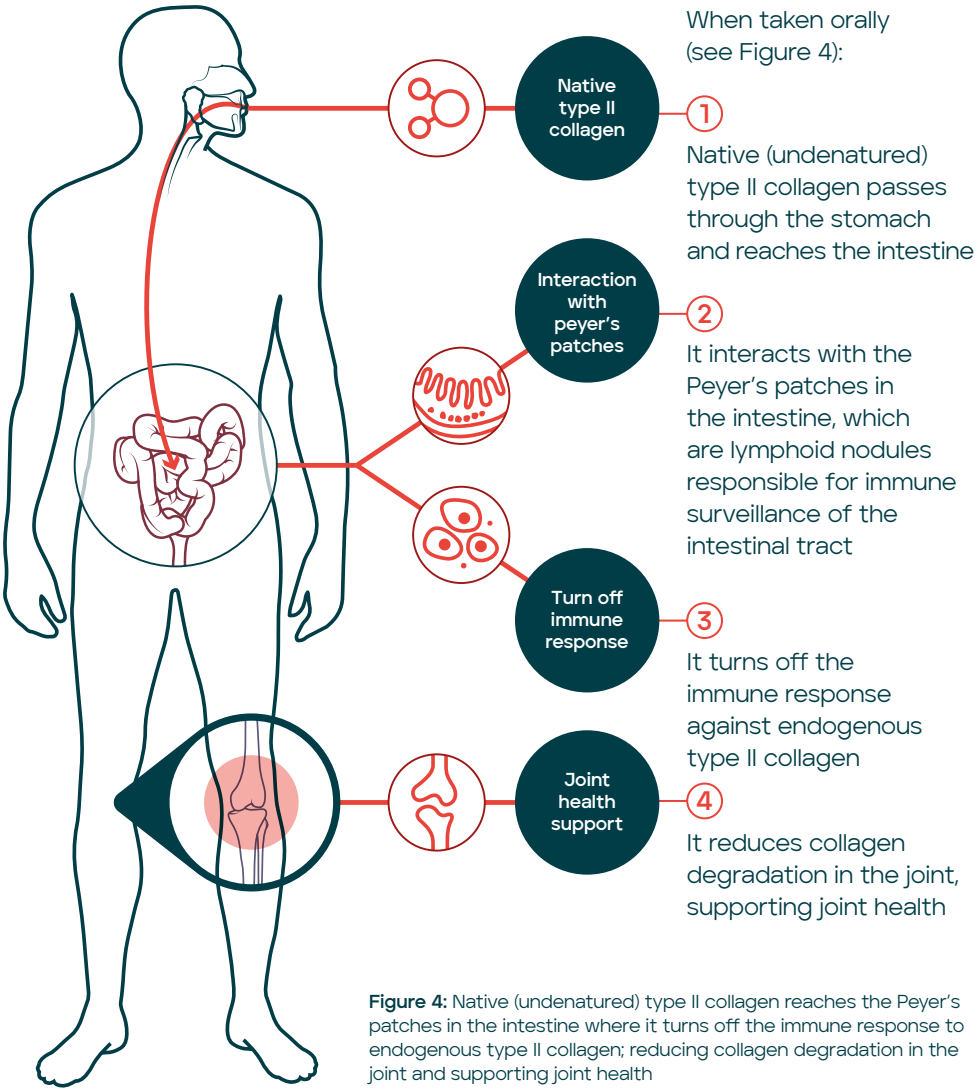
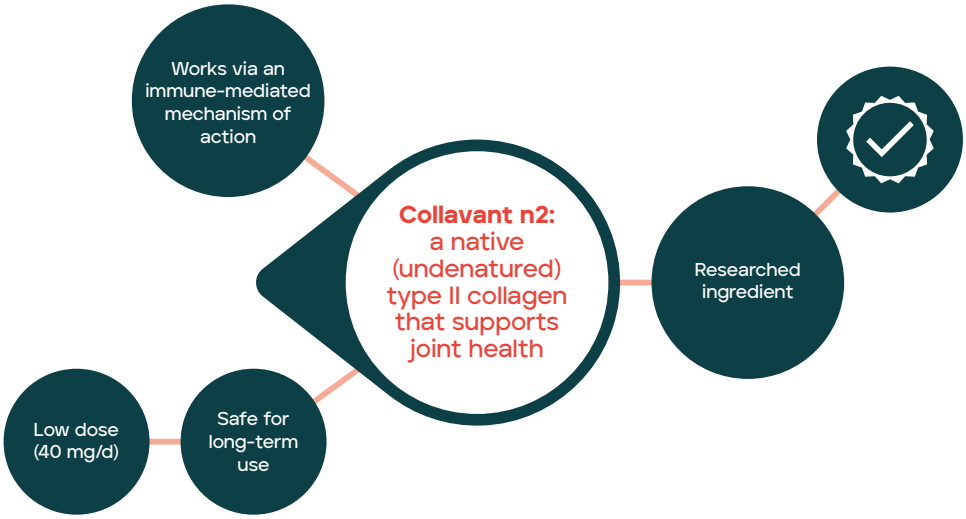


Figure 4: Native (undenatured) type II collagen reaches the Peyer's patches in the intestine where it turns off the immune response to endogenous type II collagen; reducing collagen degradation in the joint and supporting joint health

Oral tolerance is the mode of action by which native (undenatured) type II collagen works in the body.

Innovating with Collavant n2 native type II collagen

To meet growing demand for more effective, low-dose solutions in the joint health market, Bioiberica has developed Collavant n2 - a widely researched, natural-origin ingredient that supplies native type II collagen to support joint health. Extracted from chicken sternum, the manufacture of Collavant n2 is strictly controlled to maintain its characteristic triple helix structure and the biologically active epitopes of the native protein. A low dose of only 40 mg/day of Collavant n2 is required to be effective, meeting consumer demand for convenient, low-dose products and reducing pill fatigue.



Inspiring the next generation of joint health products

We're not just suppliers, we're industry partners. We provide the scientific, regulatory, industrial and market expertise to develop innovative, market-leading solutions that will help make a difference.

The science behind Collavant n2

The efficacy of Collavant n2 supplementation

Collavant n2 supplementation efficacy has been assessed in two clinical studies (one single blind trial and one retrospective trial) in patients with OA, and in two preclinical studies using animal models of OA.

Results from these studies showed that the ingredient effectively supports joint health.

1. In vivo study: Effect of native (undenatured) type II collagen in a rat model of osteoarthritis induced by MIA[10]

Objective

To evaluate the role of low doses of chicken native type II collagen in the rat model of osteoarthritis, induced by sodium monoiodoacetate (MIA).

Methods

0.3–10 mg/kg chicken native type II collagen was daily administered orally for 14 days starting from the day of MIA intra-articular injection. Glucosamine (250 mg/kg p.o.) was used as a reference compound. Pain behaviour measurements (paw pressure test; Plantar Test; Von Frey test; Incapacitance test; Animex test) were performed on days seven and fourteen. On day fourteen, plasma samples were collected to evaluate biochemical parameters.

Mannelli LDC, et al. Low dose chicken native type II collagen is active in a rat model of osteoarthritis. Osteoporosis Int., 2015, vol. 26, pg. 184.

Results

Native (undenatured) type II collagen (1–10 mg/kg) significantly reduced mechanical hyperalgesia (Figure 5 paw pressure test) on days seven and fourteen. The lower dosage was effective on day fourteen. Efficacy was comparable to those induced by 250 mg/kg glucosamine. On day fourteen, collagen counteracted thermal hyperalgesia, as measured by the Plantar Test. Moreover, collagen significantly decreased the response to mechanical sensitivity (Von Frey test) both on days seven and fourteen. As evaluated by the Incapacitance test, collagen (1–10 mg/kg) was able to prevent MIA-induced spontaneous pain. Repeated treatment with collagen improved the spontaneous mobility of the animals, as evaluated by the Animex test. Also, native type II collagen was able to prevent the MIA-dependent plasmatic increase of IL-1ß (Figure 6) and TNF-α. Finally, repeated collagen administrations reduced the degradation of endogenous collagen since the plasmatic levels of the degraded fragment C2C were significantly decreased. The stimulus to a de novo synthesis of collagen (propeptide CPII) was maintained.

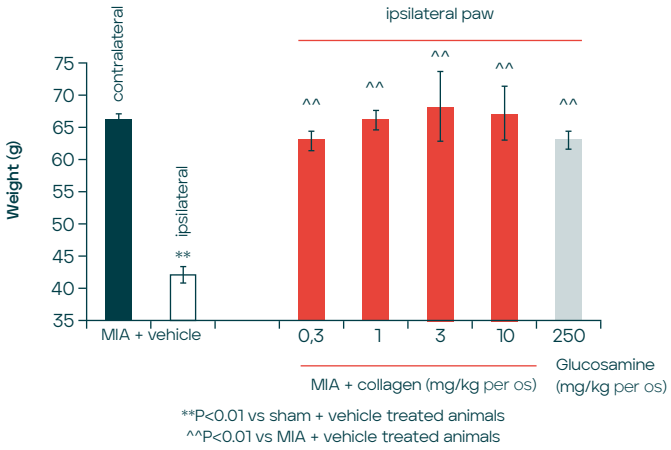


Figure 5: Paw pressure test

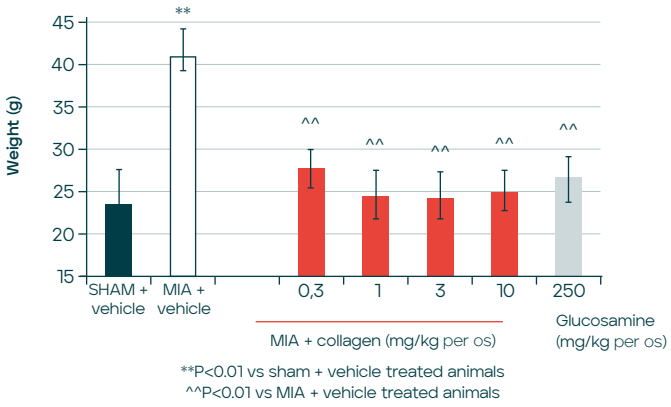


Figure 6: IL-1ßplasmatic levels on day fourteen

Conclusion:

These results describe the effects of low dosages of chicken native type II collagen by a mechanism that involves a protective effect on cartilage.

2. In vivo study: Effect of native (undenatured) type II collagen on a glycosaminoglycan's composition in a rabbit model of osteoarthritis[11]

Objective

To evaluate the effects of native type II collagen (NC) in combination with chondroitin sulphate (CS), glucosamine hydrochloride (GH) and a rooster comb extract rich in hyaluronic acid (HA) – in a rabbit model of osteoarthritis induced by anterior cruciate ligament section.

Methods

Following osteoarthritis-inducing surgery, rabbits were divided into three groups (n=18). Each group received a daily oral administration, starting on the surgery day, of the following combination: Group 0 (control group) – no treatment. Group 1 – CS (CS b-Bioactive®) + GH + HA (Mobilee®). Group 2 – CS + GH + HA + NC (Collavant n2). For cartilage, bone and synovial membrane evaluation, samples of lateral femoral condyle and synovial membrane were obtained after 28, 56 and 84 days.

Tibial plateau and femoral condyle images from Group 0 and Group 2 were obtained with a 3T MRI scanner. The non-operated knee from Group 0 was used as the healthy control.

Sifre V, et al. Macroscopic and histologic improvements in joint cartilage, subchondral bone and synovial membrane with glycosaminoglycans and native type II collagen in a rabbit model of osteoarthritis. Osteoarthritis Cartilage, 2020, vol. 28, pg. S206.

Sifre V. et al. Glycosaminoglycans combined with native type II collagen improve magnetic resonance imaging biomarkers in a rabbit osteoarthritis model. Veterinary Surgery, 2020, vol 49, pg. O238-O239.

Results

Macroscopic evaluation showed significantly improved cartilage appearance in group two when compared to the other groups in the study, and was closer to that of healthy cartilage (Figure 7). Microscopically, the assessment of articular cartilage revealed significantly better cartilage structure, chondrocyte density, subchondral bone and synovial membrane for the treated groups, compared to the control group, indicating a lower degree of degenerative changes in the treatment groups.

Histologic evaluation of the synovial membrane showed significantly lower values in Group 2 compared to the other groups; and significantly lower values in Group 1 when compared to the untreated group.

MRI evaluation showed that, in Group 0, all biomarkers in the injured knee were significantly worsened compared to the healthy one. However, Group 2 showed better results compared to the control group and values closer to the healthy ones.

Overall, Group 2's joint structures showed values closer to those of a healthy joint, followed by Group 1. Whereas, the joints in the untreated group featured more advanced degenerative process of osteoarthritis.

The main findings are summarised in Figure 7.

Groups	Treatments	Improved cartilage appearence	Improved cartilage structure, chondrocyte density, subchondral bone and synovial membrane	Improved synovial membrane	Similarity to a healthy joint
0	None	–	–	–	–
1	**CS** - CS b-Bioactive® (chondroitin sulphate) + **GH** - (glucosamine) + **HA** – Mobilee® (rooster comb extract rich in hyaluronic acid)	+	+	+	+
2	**CS** + **GH** + **HA** + **NC** - Collavant n2 (native type II collagen)	++	++	++	++

Figure 7: Summary of the main results obtained in the different study groups after 84 days

Conclusion:

This study highlights the beneficial effects of an oral combined solution of chondroitin sulphate, glucosamine hydrochloride and hyaluronic acid on joint health. Even better results were obtained when adding Collavant n2 native type II collagen.

3. Clinical study: Observational retrospective study to evaluate the therapeutic efficacy of native (undenatured) type II collagen[12]

Objective

To determine the therapeutic efficacy of native type II collagen in combination with glucosamine and chondroitin sulphate.

Methods

An observational retrospective study, one-year follow-up, on 104 patients with osteoarthritis (nodular hand OA, erosive hand OA (EOA), knee or hip OA) who were treated with glucosamine and chondroitin sulphate (GC) or glucosamine, chondroitin sulphate and collagen type II (GCC).

57 were treated with GCC and 47 with GC. Data was collected at baseline, six and twelve months: patient global assessment (VAS), C-terminal cross-linking telopeptides of collagen types I (uCTX-I) and II (uCTX-II) and radiographs (only at baseline and twelve months).

Scarpellini M, et al. Biomarkers, type II collagen, glucosamine and chondroitin sulphate in osteoarthritis follow-up: the "Magenta osteoarthritis study". J Orthop Traumatol., 2008, vol. 9, no. 2, pg. 81-87.

Results

After six and twelve months of treatment, VAS, uCTX-I and uCTX-II mean values were significantly lower than the baseline. The group that received GCC showed a similar VAS mean value after six and twelve months when compared with the group treated with GC. The uCTX-I (Figure 8) and uCTX-II (Figure 9) mean levels were lower in the GCC-treated group ($p<0.05$).

Radiological score (Figure 10) showed reduced disease progression in hand osteoarthritis after one year of treatment, especially in the GCC group ($p<0.05$).

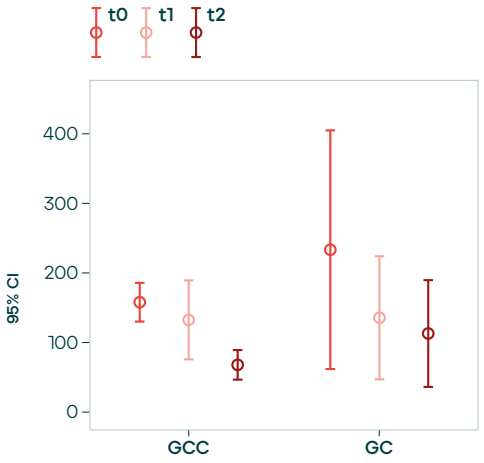


Figure 8: Urinary C-terminal cross-linking telopeptides of type I collagen in EOA group, GCC vs. GC

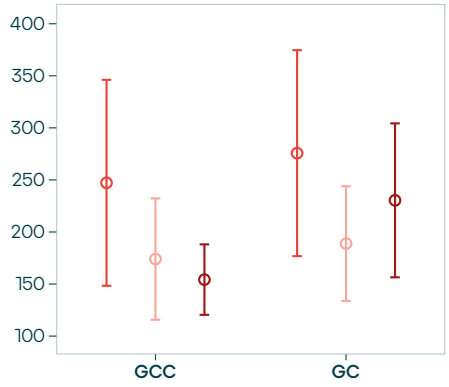


Figure 9: Urinary C-terminal cross-linking telopeptides of type II collagen in hand OA and hand EOA, GCC vs. GC

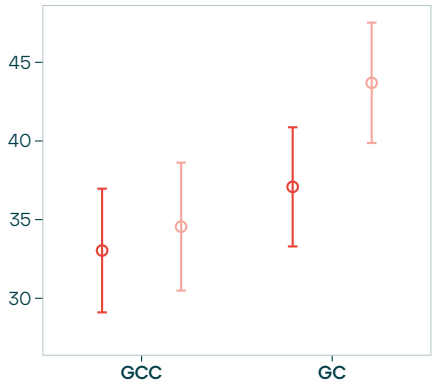


Figure 10: Evolution of radiological score in hand OA and hand EOA, GC vs. GCC

Conclusion:

The addition of native type II collagen to Glucosamine-Chondroitin (GCC group) further improved the obtained results of the Glucosamine-Chondroitin (GC) combination. The GCC-treated group showed better results in reducing collagen destruction and osteoarthritis progression compared to the GC-only group.

4. Clinical study: Randomised controlled study to assess the efficacy of native (undenatured) type II collagen on the symptoms and biomarkers of cartilage degradation[13]

Objective

To evaluate the effect of native type II collagen on knee OA when used concomitantly with acetaminophen.

Methods

39 patients with knee OA were included and randomly distributed into two groups: one treated with 1500 mg/day of acetaminophen (group AC; n=19) and the other treated with 1500 mg/day of acetaminophen plus 40 mg/day of Collavant n2 (group AC+CII; n=20) for three months. Visual Analogue Scale (VAS) for pain at rest and during walking, Western Ontario McMaster (WOMAC) pain, WOMAC function, and Short Form-36 (SF-36) scores, were recorded.

Bakilan F, et al. Effects of native type II collagen treatment on knee osteoarthritis: a randomised controlled trial. Eurasian J Med., 2016, vol. 48, no. 2, pg. 95-101.

Results

After three months of treatment, significant improvements compared to baseline were reported in pain, function and quality of life and as measured by VAS walking (p<0.001), WOMAC pain (p=0.003), WOMAC total (p=0.004) (Figure 12), WOMAC physical function (p=0.016) and subscales of SF36 in the AC+CII group. Only some subscales of the SF-36 survey and VAS walking showed improvement in the AC group. Comparisons between the groups revealed a significant difference (p=0.002) in VAS walking score in favor of the AC+CII group, when compared to the AC group (Figure 11). Additionally, a statistically significant (p=0.004) improvement in WOMAC score was observed versus baseline.

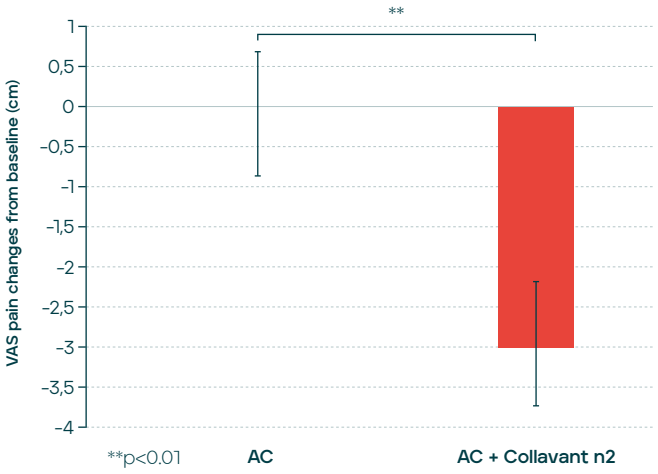


Figure 11: VAS pain changes with Collavant n2 supplementation

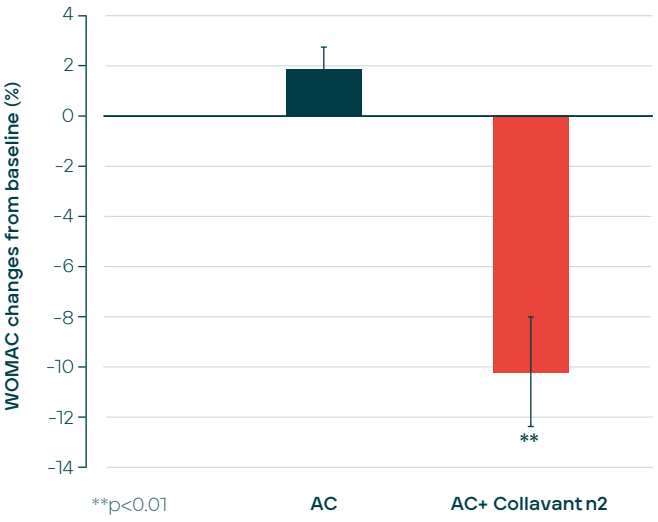


Figure 12: Total WOMAC evolution evaluating knee function with and without Collavant n2 versus baseline.

Conclusion:

These results suggest that native type II collagen combined with acetaminophen is superior to only acetaminophen in patients with knee osteoarthritis.

5. Clinical study: Multicentric, observational study to evaluate the efficacy of native (undenatured) type II collagen in combination with the herbal extract, *boswellia serrata*[14]

Objective

To investigate the efficacy and safety of a propriety formulation of a *boswellia serrata* extract in combination with type II collagen in OA patients.

Methods

40 patients with knee OA were recruited in a multicentric clinical trial across three different sites. Patients were instructed to consume one oral capsule containing 40 mg Collavant n2 and 100 mg *boswellia serrata* (Aflapin®, Laila Nutraceuticals) daily for three months. The efficacy parameters assessed were Visual Analog Scale (VAS) for pain and Western Ontario McMaster (WOMAC) for pain, function and stiffness. To determine safety of the combination, subjects were asked to report any adverse events during the intervention period.

Jain A, et al. AflaB2® and osteoarthritis: a multicentric, observational, post-marketing surveillance study in Indian patients suffering from knee osteoarthritis. International Journal of Research in Orthopaedics, 2021, vol. 7, no. 1, pg. 110-115.

Results

After three months of treatment, patients showed significant improvements across all parameters compared to the baseline. Statistically significant improvements were identified in the VAS ($p<0.01$) and WOMAC ($p<0.001$) scales from day five of the intervention. VAS and WOMAC scales continued to decrease consistently during the period in which supplements were taken (Figures 13 and 14).

When observing WOMAC subscales specifically, pain ($p<0.01$) and physical function ($p<0.001$) scores improved from day five, and stiffness ($p<0.01$) from day 15. No significant side-effects were reported during the study.

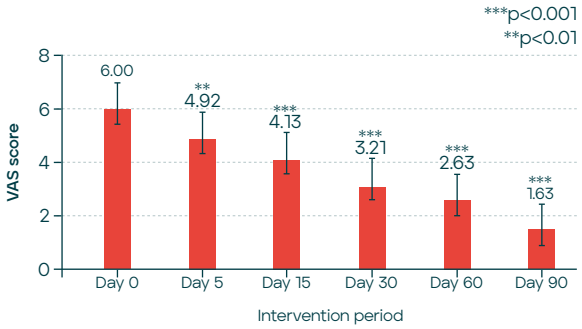


Figure 13: Effect of a Collavant n2 and *boswellia serrata* supplement on VAS scores versus baseline.

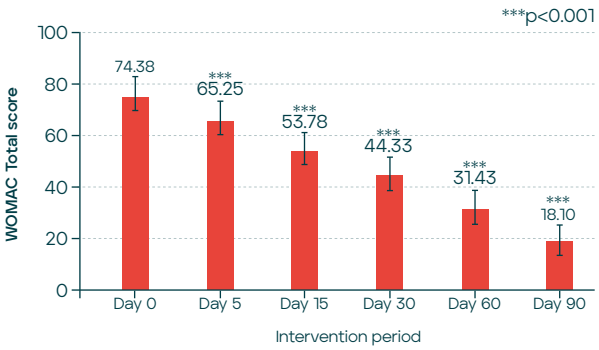


Figure 14: Effect of a Collavant n2 and *boswellia serrata* supplement on WOMAC scores versus baseline.

Conclusion:

This study highlights the efficacy and safety of combined oral supplementation of Collavant n2 and *boswellia serrata*, which was shown to significantly alleviate OA symptoms in just five days.

References

1) National Center for Health Statistics, United States, 2011, Hyattsville, MD, 2012.
2) Estudio MMYA, Rodriguez Bueno E. et al., Congreso AEEM, 2010.
3) Op. cit. (National Center for Health Statistics).
4) Cheng et al., "Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor?", Journal of clinical epidemiology, vol. 53, pg. 315-322, 2000.
5) Mordor Intelligence, Bone and joint health ingredients market - growth, trends and forecast (2019-24), [report], 2018.
6) SPINS Natural Enhanced Channel and SPINS Conventional Multi Outlet (powered by IRI) | 52 Weeks Ending 4-18-2021.
7) M. Shoulders et al., 'Collagen structure and stability', Annu Rev Biochem., vol. 78, pg. 929-958, 2009.
8) Kandahari, A. M. et al., 'Recognition of immune response for the early diagnosis and treatment of osteoarthritis'. J. Immunol. Res., pg. 1-13, 2015.
9) Park et al., 'Type II collagen oral tolerance; mechanism and role in collagen-induced arthritis and rheumatoid arthritis', Modern Rheumatology, vol. 19, no. 6, pg. 581-589, 2009.
10) Mannelli, L.D.C. et al., 'Low dose chicken native type II collagen is active in a rat model of osteoarthritis', Osteoporos. Int.,. vol. 26, pg. 184, 2015.
11) Sifre V, et al. Macroscopic and histologic improvements in joint cartilage, subchondral bone and synovial membrane with glycosaminoglycans and native type II collagen in a rabbit model of osteoarthritis. Osteoarthritis Cartilage, vol. 28, pg. S206, 2020.
12) Scarpellini, M. et al., 'Biomarkers, type II collagen, glucosamine and chondroitin sulfate in osteoarthritis follow-up: the "Magenta osteoarthritis study"', J. Orthop. Traumatol., vol. 9, pg. 81-87, 2008.
13) Bakilan, F. et al., 'Effects of Native Type II Collagen Treatment on Knee Osteoarthritis: A Randomized Controlled Trial', Eurasian J. Med., vol. 48, pg. 95-101, 2016.
14) Jain, A et al., 'AflaB2® and osteoarthritis: a multicentric, observational, post-marketing surveillance study in Indian patients suffering from knee osteoarthritis', International Journal of Research in Orthopaedics, vol. 7, pg. 110-115, 2021.

Notes

Notes

Notes

About Bioiberica

Bioiberica is a global Life Science company with more than 45 years' experience in the identification, extraction and development of biomolecules of high biological and therapeutic value for the pharmaceutical and nutraceutical industries. With a portfolio of scientifically-backed ingredients inspired by the latest consumer trends, Bioiberica Healthcare serves the mobility, digestive health and skin & beauty markets.

To innovate in the joint health market using Bioiberica's Collavant n2 native type II collagen, contact us today.

Visit: **www.bioiberica.com**

Email: **healthcare@bioiberica.com**

Call: **+34 93 490 49 08**

Y405598/0322

Collavant n2
Native (undenatured) type II collagen

Bioiberica
Taking life science further