Joint Flex Plus (BioCell Collagen)

Goal

Support skin and joint health including relief from age-related or overuse minor joint pain and helping restore or maintain youthful skin appearance.

Supply a joint and skin structure and function supporting dietary supplement, trade name BioCell Collagen (BC), composed of naturally occurring hydrolyzed collagen type II peptides, chondroitin sulfate and hyaluronic acid, not available from the diet, and clinically established to support the health of collagenous tissues (tendon, ligament, cartilage, skin and bone), especially joints and skin. In joints, the ingredients work to improve the ratio of the normal biological processes of cartilage degradation and synthesis to favor synthesis through supplying building blocks, potentially stimulating chondrocytes/collagen production, and supporting lubrication to help enhance or maintain healthy joint tissue and function.

The contents of JointFlexPlus (JFP) are contained in a unique matrix (not individual ingredients) designed to increase the supply of the necessary building blocks of connective tissues in joints and skin to support exercise or injury recovery and restore the natural age-related losses that can otherwise lead to compromised mobility, joint pain and weakened skin health. Supplementing BioCell Collagen® may also help recovery from specific activities that severely challenge connective tissues (e.g., jumping, fast direction changes, etc.) and attenuate performance decrements thus possibly reducing risk of injury. In skin, the ingredients help to protect against photoaging and maintain the integrity of the extracellular matrix in the dermis below the skin, which is crucial for youthful skin appearance, helping reduce visible aging signs such as wrinkles and fine lines as well as the dehydration and scaling of the skin.

Rationale

Collagen, hyaluronic acid, and chondroitin sulfate are the primary active constituents in the tissues of joint cartilage and skin. The tissue's content/production of these components decrease with age and is compromised by challenging movements and environmental insults. Direct replenishment or endogenous stimulation through supplementation of these critical building blocks in a micronized form mimicking the fundamental molecular composition of human articular cartilage and dermal matrix, can help restore tissue concentrations to more youthful levels to promote joint health, skin beauty and aid in protection and recovery of musculoskeletal tissue during challenging sports activities.

Collagen is the most abundant protein in the human body (~30% of total body proteins) and is the primary structural protein in the extracellular matrix (ECM)* of connective tissues such as cartilage, bones, ligaments, and skin.[1,2] Beyond collagen's functions in muscle, bone and blood, collagen is responsible for the health of joint cartilage (padding that protects bones at the joints) and allows the youthful elasticity in skin, the body's largest organ. The body's collagen production decreases with aging (see Figure 1)[3] and compromised by injuries, sun, and excess activity, leading to decreased mobility, joint pain, and aging skin appearance (e.g., wrinkling/lines), spawning the use of specific collagen peptides/supplements to improve the collagen content of respective tissues, or help offset the age-related reduction in synthesis through the delivery of stimulating building blocks, such as collagen type II and glycosaminoglycans (hyaluronic acid, chondroitin sulfate, etc.,) the primary components of connective tissue.[4,5,6] Further, collagen peptides are often used to hasten recovery from activities that severely challenge connective tissues.[7,8,9]

***Extracellular matrix** (ECM): The non-cellular component in all tissues and organs providing essential physical scaffolding for the cellular constituents and initiates biochemical and biomechanical signals that are required for tissue morphogenesis, differentiation, and homeostasis.

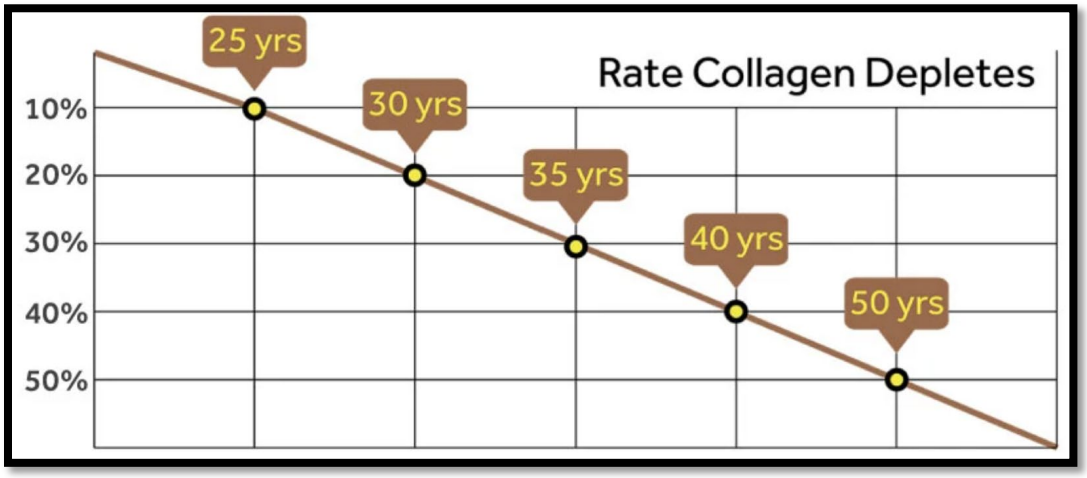


Figure 1 – Rate Collagen Depletes by Age[3]
Annual decline of 1-1.5% (range is dependent on genetics and environmental/lifestyle insults) in production and overall collagen content starting around the third decade of life (women lose up to 30% during the first five years of menopause).[3]

Background – Collagen, Hyaluronic Acid (HA), Chondroitin Sulfate (CS) and Extracellular Matrix (ECM) in Joints

Collagen

The most abundant protein in the human body; responsible for the health of joint cartilage; and decreases with age or compromised from injury

Collagen protein (CP), is not a complete protein such as dairy, fish, fowl, or beef, as it lacks tryptophane and cysteine, and gram for gram compared to complete proteins, CP is very low in essential amino acids (EAA) and therefore not a supplement used for maximizing muscle protein synthesis. [10,11,12,13] However, CP is high in glycine (33%), proline, hydroxyproline (22%), hydroxylysine and arginine, the primary amino acids (AA) found in collagenous structures. CP's stable triple helix structure allows its unique biomechanical properties, including the ability to withstand/resist stretching or tensile forces and makes it the primary structural and functional component of connective tissues.[1,4] There are many types of collagen proteins (~28-40) but there are four (type I, II, III and IV) primary types.[1,4,14]

- Type I forms fibers found in most connective tissues with high concentrations in ligaments, tendon, bone, and skin.
- Type II forms fibers (less organized than type I) found mainly in cartilage.
- Type III forms fibers thinner than type I and make up reticulin fibers in organs and help organize their cells.
- Type IV forms branched networks and helps organize the basement membrane.
- Collagen type I and II are the most important structural and functional components of the ECM of tendons, ligaments and cartilage.[15]

Extracellular Matrix (ECM)

The non-cellular component in all tissues and organs providing essential physical scaffolding for the cellular constituents and initiates biochemical and biomechanical signals that are required for tissue morphogenesis,

differentiation, and homeostasis - all cells need to attach to their respective extracellular matrix to grow and multiply.[16]

Articular Cartilage ECM

Articular Cartilage (AC) is specialized connective tissue (made up of type II collagen and chondromucoprotein*) of diarthrodial (moveable) joints that primarily provides a smooth, lubricated surface for articulation and facilitates the transmission of loads with minimal friction[17]

*Ground substance (the fluid or solid material) that occupies the space between the cells and fibers of cartilage.

The only cells in AC are specialized cells called chondrocytes** (and precursor chondroblasts) and produce large amounts of collagenous ECM. Chondroblasts are responsible for the secretion and maintenance of the ECM.[18] AC ECM plays a crucial role in regulating chondrocyte functions via cell-matrix interaction, organized cytoskeleton, and integrin-mediated signaling (see Figure 2 below).[19] Cartilage chondrocyte production of ECM components is compromised by aging, injury and activity factors leading to the supplementation of these component signaling and building blocks to help restore ECM/cartilage integrity.[6,7,8,20,21]

**Chondrocytes are cells that synthesize and turnover a large volume of ECM components such as collagen, glycoproteins, proteoglycans, and hyaluronan[22]

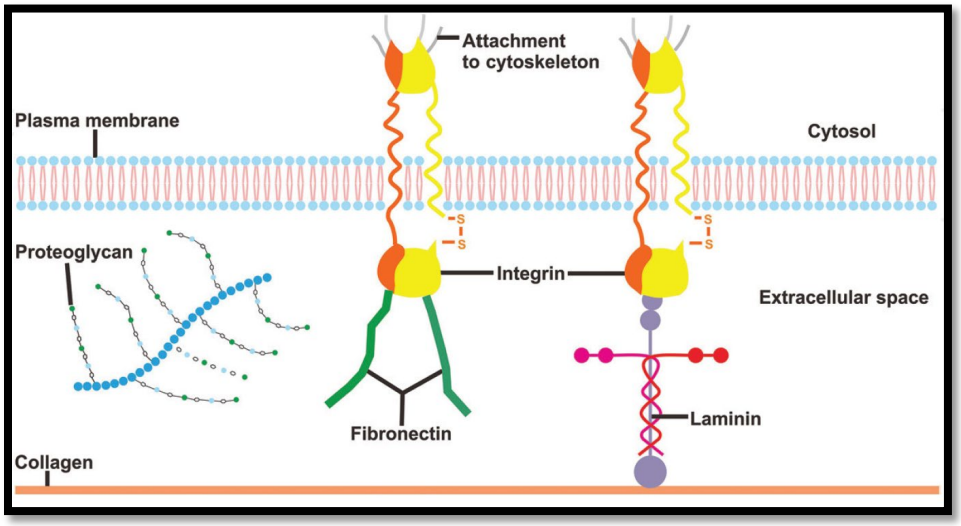


Figure 2 - Structure of the ECM that mainly contains collagen fibers. The glycoproteins act as an adhesion molecule, such as integrin family fibronectin and laminin, which conduct cell attachments to the ECM via binding to collagen in the ECM and integrin. The intracellular part of integrin highly associates with the cytoskeleton thus may promote to anchoring the cell.[19] Figure used via open access.

The AC ECM (area between cells) is a non-cellular structure that regulates most all cellular functions including cartilage synthesis, degradation, and tissue homeostasis. The structural network of the ECM continuously undergoes remodeling mediated by signals (e.g., decreasing or increasing collagen concentrations) of tissue specific cells (e.g., cartilage, tendons, etc.), which trigger the anabolic and catabolic processes as necessary to achieve ECM and related tissue homeostasis including the ECM macromolecule composition (e.g., collagen, glycosaminoglycans, etc.).[23] Therefore, ECM is the core constituent of connective tissues like cartilage that

regulates the tissue structure, mechanical strength, maintenance, and organization to maintain homeostasis including supporting the tissues growth mechanism, regenerative, and healing processes.[20]
Cartilage ECM is composed primarily of type II collagen and large networks of proteoglycans (PGs) that contain glycosaminoglycans (GAGs) such as hyaluronic acid (HA) and chondroitin sulfate (CS). The major biological function of proteoglycans comes from the physicochemical characteristics of the GAG component of the molecule, which provides hydration and swelling pressure to the tissue enabling it to withstand compressional forces.[21]
In summary, loss of cartilage integrity (more degradation than synthesis or damage), naturally happens in aging, injury or from excessive/specific activities. In the former, this is generally due to a reduction in collagen and other cartilage component production (e.g., GAGS). In the latter, natural production/synthesis may not keep pace with activity-induced degradation. The ECM is the core constituent of connective tissues like cartilage that controls the tissue's structure and health. Therefore, recently cartilage ECM has been a therapeutic target to support joint health because proper stimulation and maintenance of the cartilage ECM is critical to maintaining youthful production and distribution of collagen and supporting bio-actives such as HA and CS that make up joint/articular cartilage and give it its special cushioning properties.

Type II Collagen (COLII)

Cartilage ECM is composed primarily of the network type II collagen (COLII) and an interlocking mesh of fibrous proteins and proteoglycans, which are composed of a protein core and glycosaminoglycan chains such as HA and CS. The ECM and two-thirds of dry mass in adult articular cartilage are polymeric collagen with COLII being the primary molecular component. The age-related decrease in collagen production has inspired the use of collagen supplementation to help restore ECM components/function[4,5,6,7,8,9,24]

As described above, the health of AC is dependent upon the maintenance of the ECM made of two main components, proteoglycans (containing HA and CS) and collagens as shown in Figure 3A. COLII is the predominant type in cartilage. COLII forms a 3D fibrous network which provides tensile stiffness and strength to cartilage and provides the basic architecture to the tissue. Aggrecans (and other types of proteoglycans) are embedded within this fibrous network, providing compressibility and elasticity to the tissue.

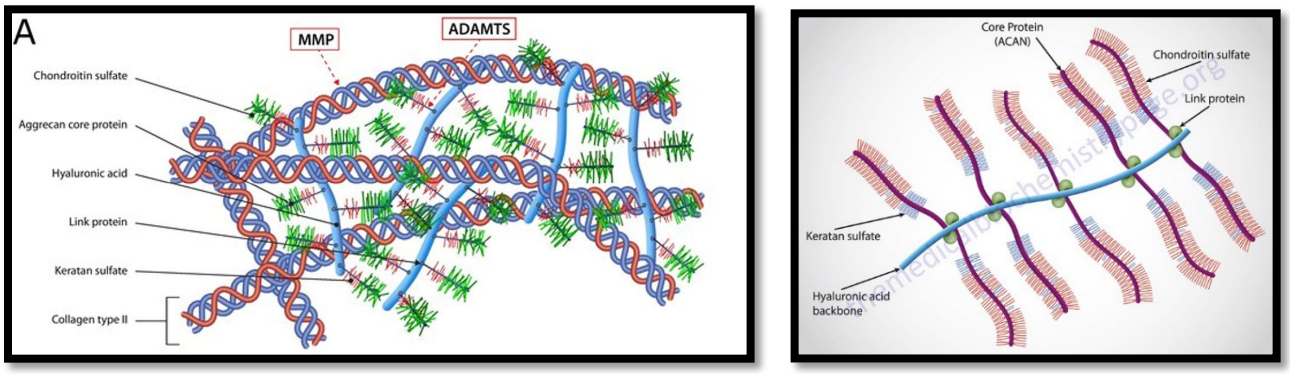


Figure 3A - Joint cartilage ECM showing a healthy network of proteoglycan aggregates entangled with COLII fibers that allows the cushioning of forces that supports pain free normal mobility. Aggrecan is the major proteoglycan (PG) in AC, with HA and CS existing as the major glycosaminoglycan portion of these PGs. The right pane highlights HA and CS in the ECM.[25]

Chondrocytes are responsible for the synthesis, organization, and maintenance of the ECM components (e.g., COLII, HA, CS). Communication between chondrocytes and the ECM determine degradation or synthesis. Aging/damage can alter the sensitivity of chondrocytes to regulatory signals.[26] This starts a progressive imbalance between degradation and synthesis/regeneration, leading to a marked decrease in the content of type II collagen and degradation of PGs/GAGs in the ECM, eventually leading to cartilage damage (see Figure 3B).[26,27,28]

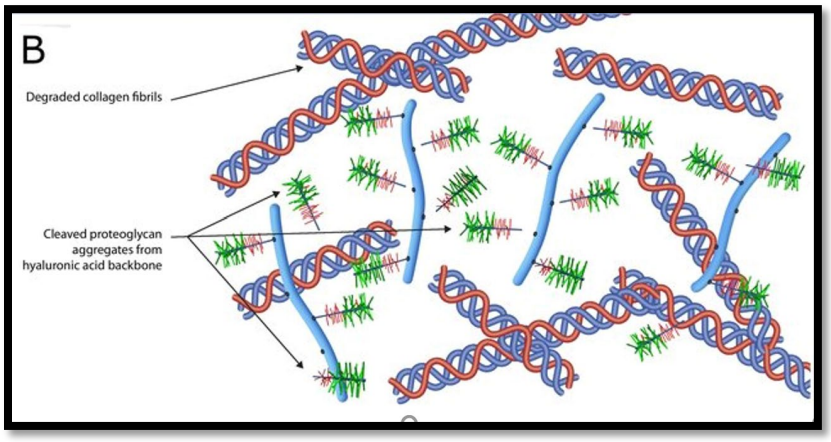


Figure 3B - Cartilage matrix changes in aging defined by degradation of proteoglycans and cleavage of COLII fibers by ADAMTS and MMPs, respectively or an unbalance in synthesis and degradation cycle of the ECM components.[25,28]

Specific low molecular weight collagen peptide supplements are manufactured so that digestion, absorption, and subsequent transit of the fragments arrive at the target tissues (e.g., joint area, skin, etc.) to improve the collagen (primarily COLII in joints) content when age or injury related decreases occur that would otherwise negatively affect ECM homeostasis and eventually leading to constrained mobility or discomfort.[4,29,30,31,32,33,34,35,36] To be sure, supplementing these specialize collagen peptides with supporting ECM constituents have been shown to be effective in damaged/aging joints for improving mobility and pain reduction based on both total WOMAC* index and VAS** score.[4,5,6,7,8,9,24,36,37,38,39]

*The WOMAC (Western Ontario and McMaster Universities) index is used to assess patients with degeneration of the hip or knee using 24 parameters. It can be used to monitor the course of the problems/pain/function or to determine the effectiveness of anti-rheumatic therapies.
**VAS: Visual analogue score for pain

Hyaluronic Acid

HA (also called hyaluronan) is present in all connective tissues and organs, including the skin and joints (essential component of synovial fluid). HAs primary function is to hold water, keeping tissues lubricated thus acting as an effective lubricant in the biomechanics of moving joints,[40] and is often supplemented to support skin and joint health.[41,42]

HA is abundant in the ECM of adult soft connective tissues such as joint cartilage. Because of HA's carboxyl groups (and does not contain any sulfates), it is negatively charged, hydrophilic (strong affinity to water), and its size allows it to form viscous networks.[43] HA's properties permit it to hydrate the ECM and regulate the tissue homeostasis and resistance to compression forces.[44] As Figure 3A depicts, the PGs in the ECM interact with HA (GAG portion) establishing unique molecules responsible for the gel-like matrix and overall stabilization of ECM

structure.[25,28] Further, HA functions as a signaling molecule cooperating with its binding proteins and regulates cell adhesion, migration and proliferation toward homeostasis. Additionally, HA is an essential component of synovial fluid, where it contributes to its fundamental role as a lubricant for the joints.[45] HAs mechanisms of action, named above, in support of joint (and skin), structure, function and health, combined with its injury-induced and natural age-related decreasing content in the human body, make HA a popular therapeutic agent for use and study in preserving or restoring cartilage tissues.[28,45,46,47]

Chondroitin Sulfate (CS)

Like HA, CS plays a major role in the structure and function of AC, as it is also a primary active molecule in the ECM that gives AC its special physicochemical characteristics that allow it to withstand compression forces. Natural production of CS decreases in aging and is *inefficient during injury,* ***[48,49,50,51] making supplementation commonplace, to at a minimum deliver a prophylactic effect.***[52,53,54,55,56,57,58]

Shown in Figure 4, CS is one of five classes of glycosaminoglycans along with hyaluronic acid, heparan, keratan, sulfate and dermatan sulfates.[59] Glycosaminoglycans are long, linear polysaccharides that possess a repeating disaccharide unit with various sulfated residues (not in HA) that regulate their biological functions.[60] CS disaccharides can have different amounts and patterns of sulfation. Each CS chain may contain a mixture of disaccharides and therefore vary in length and molecular weight.[61,62] To be sure, the molecular weight of naturally occurring CS can range from 50-100 kDa.[63] This variation including charge density can affect its chemical properties, thus biological/pharmacological activities including absorption and transport kinetics.[50,63,64,65] Like HA, CS supplementation is commonly used to support its activities in AC. On damaged/aging joint tissues, CS supplementation has been shown to alter the chondrocyte death process, improve the anabolic/catabolic balance of the extracellular cartilage matrix, reduce some pro-inflammatory and catabolic factors, and decrease the resorptive properties of subchondral bone osteoblasts.[50,53] Additionally, supplementation has demonstrated efficacy in reducing the rate of joint space narrowing, which may also translate to less pain and improved mobility overtime.[52,53,66,67,68,69, 70,71]

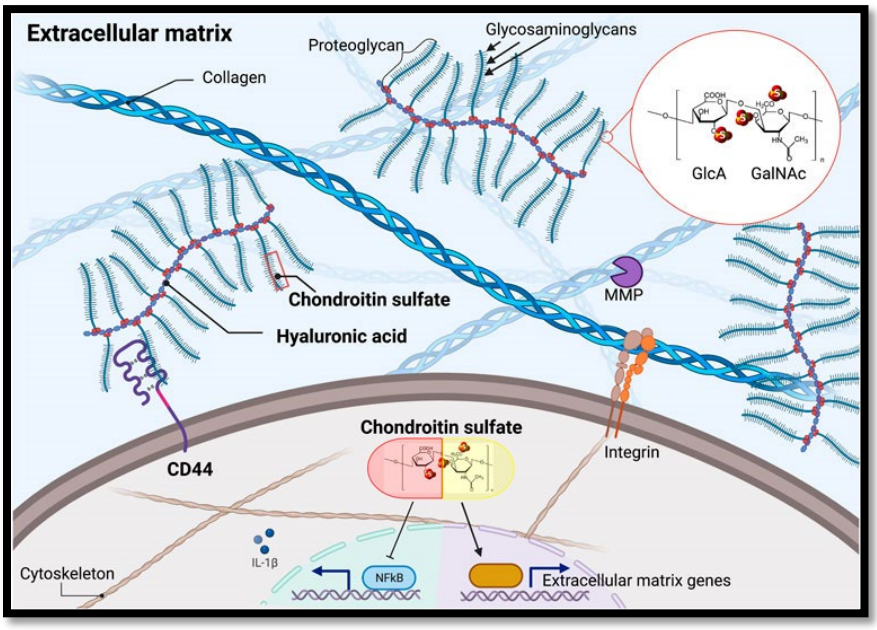


Figure 4 from Makami et al.[72] CS in the extracellular matrix and cellular effects of supplementation. CS polymers are the building blocks of proteoglycans that can be attached to the HA polymers. Supplementation of CS blocks NF-kB mediated inflammation and stimulates ECM homeostasis. MMP = matrix metalloproteinase.[50]

Mechanisms of Action

Mechanisms of action of CS include an inhibiting effect on the catabolism of proteoglycans and collagen,[73,74] thus promoting/restoring ECM protein homeostasis, in part by affecting the biosynthesis and degradation of chondroitins and enzymes that remodel the ECM.[53,75] To be sure, CS supplementation has demonstrated the ability to stimulate/facilitate the synthesis of extracellular matrix active molecules including HA,[56,76,77] and shown to inhibit cartilage destruction, while stimulating PG production in connective tissues.[65,73,78,79]

There is also strong evidence that endogenous CS is necessary to suppress inflammation common in aging and a known contributor in ECM degradation. CS supplementation can reduce chronic inflammation as shown by Navarro et al., where they demonstrated a reduction in C-reactive protein concentration (inflammation biomarker) in supplemented healthy adults. Additionally, CS supplementation can reduce levels of inflammatory-associated proteins (e.g., metalloproteinases [MMP shown in **Figure 4**]) that can damage ECM.[80,81, 82,83] According to the Ewald Review, "Drug Screening Implicates Chondroitin Sulfate as a Potential Longevity Pill" (recommended reading to health professionals interested in more on CS in overall health), actionably, CS inhibits translocation of NF-ĸB, thus decreasing NF-ĸB downstream signaling leading to lower levels of pro-inflammatory cytokines and enzymes, such as IL-1β, IL-6, TNF-α, Cox-2, and Nos-2.[50,84,85] Though doses in clinical trials vary, orally ingested CS, as referenced/discussed above, can reach target tissues including skin and joints.[52,53,54,55,56,57,58,86]

In summary, CS supplementation may support joint and skin health through: 1) its ability to prolong and possibly restore ECM homeostasis/components; 2) inhibit damaging inflammation, both mechanisms that may also overlap, and 3) overcoming a dietary deficiency of sulfur-containing amino acids, which are essential building blocks for cartilage extracellular matrix molecules[53,87]

Overall Visual Summary

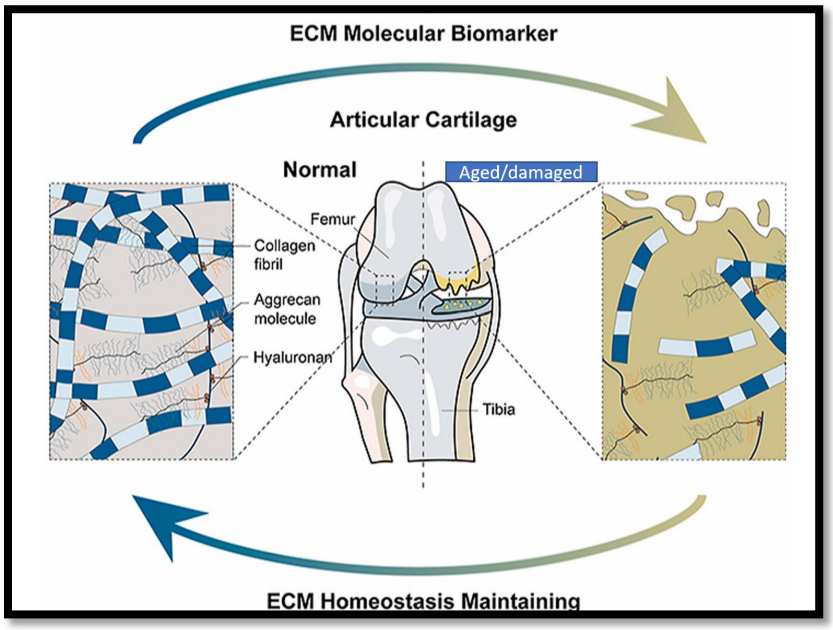
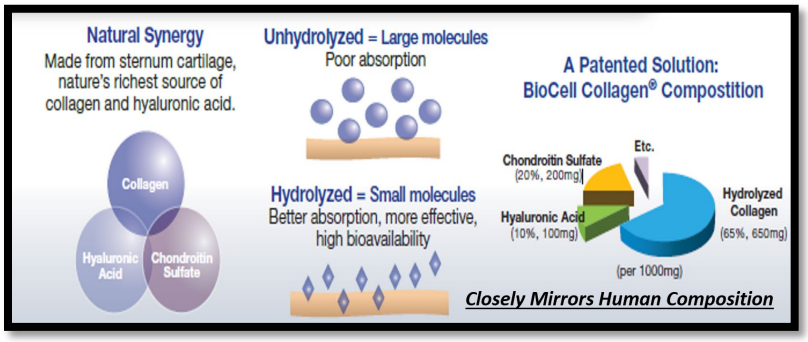


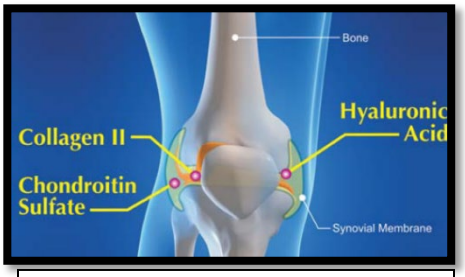
Figure 5 - The regulation of cartilage extracellular matrix homeostasis in joint cartilage degeneration and regeneration.[88] Goal of non-medical treatments is to restore or maintain ECM homeostasis.

JointFlexPlus – BioCell Collagen (BCC)

Micronized (low molecular weight) collagen peptides and GAGs derived from cartilage ECM, BCC is composed of naturally occurring hydrolyzed collagen type-II peptides, hyaluronic acid, and chondroitin sulfate in a unique natural matrix that mimics the composition of human articular cartilage. The unique patented size and natural synergistic blend of these building blocks allow these bio-actives passage to, and activity in, the target tissues such as skin and joints.

As described above in the individual sections on COLII, CS, HA and ECM, proper production/extraction and ingestion (e.g., sized, weighted, synergy etc.) of these molecular bioactive building blocks of collagen and GAGs, can help them reach the target tissues and address the natural or injury induced degradation/loss of these molecular constituents of the ECM.[4,5,6,7,8,9,38,39,40,41,89,90,91,92] Therefore, regular oral delivery of BCC's properly sized and synergistic molecules (see Figure 6) may offer a protective effect and assist in counteracting negative consequences of aging including visible skin changes and joint discomfort.[5,9,37,90,93,94,95]





Healthy knee joint showing nutrient distribution in cartilage, synovial fluid & connective tissues

Figure 6 - BCC is made from pure dietary chicken sternal cartilage (CSC) that is free from hormones and antibiotics. CSC closely mimics the composition of human cartilage rich in type II collagen, CS and HA. Extracting exclusively from cartilage eliminates the risk of potential contamination. BCC uses a patented manufacturing procedure that includes filtration, purification, concentration, hydrolysis, and sterilization, to ensure consistent quality and safety. BCC is non-GMO and free of gluten, soy, shellfish, fish, egg, milk, peanuts, and sugar. BioCell Technology manufactures BioCell Collagen in the USA and Germany.[96]

Unique Molecular Structure of BCC

In joints, BCC provides building blocks for human collagen, HA and CS production to help offset aging and excessive activity losses that leads to pain or compromised mobility. BCC's success in supporting ECM homeostasis (balancing degradation and synthesis) may be from its unique composition that closely resembles the fundamental composition of these molecules in human AC. Therefore, the size and synergy of BCC's biomolecules likely plays a major role in its efficacy demonstrated in multiple clinical trials.[5,9,37,90,93,94,95]

BCC is derived exclusively from hormone and antibiotic free chicken sternal cartilage, which is a rich source of collagen type II, HA and CS, mirroring the fundamental composition of human AC (Figure 6). Cartilage is the better source of cartilaginous building blocks because it is free from blood supplies; meaning it does not contain blood, lymphatic vessels, or capillaries like other collagen-rich animal parts (e.g., hides, bones, skin, and scales). Therefore, extracting exclusively from cartilage eliminates the risk of potential contamination (see Figure 6 narrative). Further, BCC's patented manufacturing procedure remarkably reduces the size of all its biomolecules making them highly absorbable and available to the target tissues.[96] And finally, the ingestion of BCC has been shown clinically to boosts levels of all three major collagen types (I, II, & III).[5,96]

Mechanisms of Action

BCC should be thought of as one compound made up of naturally occurring COLII, HA, and CS. Based on animal studies and BCC's seven clinical investigations and trials, mechanisms of action beyond providing these building blocks, are suggested to be that these properly sized/ratio of components in BCC can also stimulate chondrocytes (cartilage producing cells) and fibroblasts (skin producing cells), while inhibiting hyaluronidase, the enzyme that degrades HA. [5,9,29,30,37,89,90,93,94,95,97,98,99,100,101] Loss of HA contributes to aging of the skin and loss of viscoelasticity of joint synovial fluid.[25,28,45,46,47] Following challenging exercise, BCC has also been shown to attenuate muscle damage biomarkers including creatine kinase, lactate dehydrogenase, and C-reactive protein that indicate progressive connective tissue damage, supporting the compounds effective mechanism of action named here.[9]

Bioavailability

As discussed throughout this paper, the native forms of collagen and GAGs are too large to be properly absorbed following ingestion and therefore must be properly extracted and sized to reach the target tissues,[4,6,8,24,30,31,32,33,34,35,36,37,38,39] which is accomplished by the BCC manufacturing process that reduces them into very low molecular weight forms while maintaining the natural individual ingredient synergy and ratio.[96] The positive results of the seven clinical investigations supports BCC's bioavailability or what is also known as functional availability (beyond absorption to be active at the target tissues). [5,9,37,90,93,94,95] Additionally, depicted in Figure 7, in a 28-day bioavailability study of 1,500 mg/day of BCC in human subjects, it was demonstrated that BCC elevated HA blood levels 60 times at steady state over baseline[96]

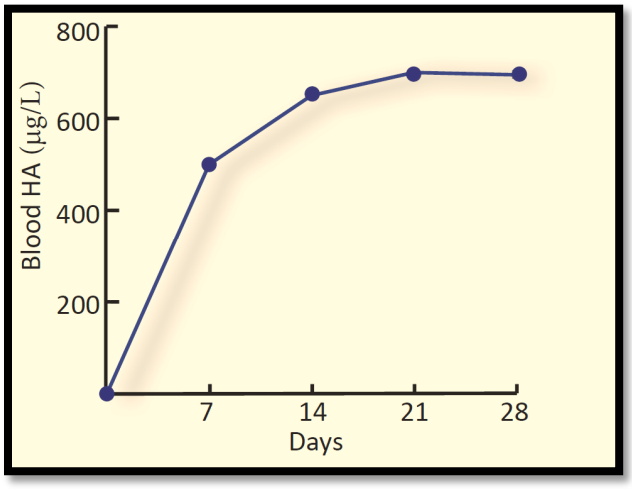


Figure 7 – Hyaluronic Acid (HA) Bioavailability at Steady State[96]

BCC Joint Studies

Figure 8 from unpublished data, shows the outcome of a human clinical study. 89 subjects suffering from pain caused by various joint-related conditions including joint discomfort ingested two grams of BCC daily for 45 days. There was a continuous increase in the number of subjects who reported increases in joint comfort/mobility. 89% (80 of 89) of the BCC group experienced joint improvements whereas only one in the placebo group had improved joint comfort.[93]

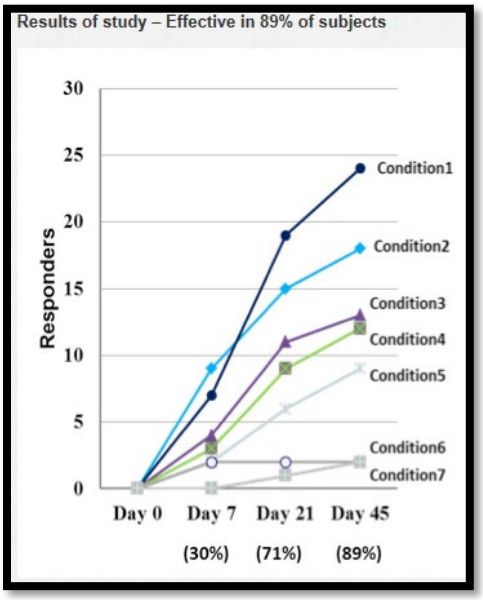


Figure 8 - Continuous increase in the number of subjects (up to 89%) who reported increases in joint comfort/mobility overtime. [93]

As a follow up study in 2004 and presented at the international conference of Experimental Biology in 2004, a randomized double-blind placebo-controlled trial of 16 subjects with joint damage of the knee or hand used 1,000 mg twice daily of BCC for two months. [94] As portrayed in Figure 9 compared to placebo the intervention group significantly reduced joint discomfort as much as 40% at the end of the 8-week study.[94] Further, the BCC subjects experienced significant improvement in all WOMAC subscales and in total WOMAC* score with no adverse events related to the study compounds.

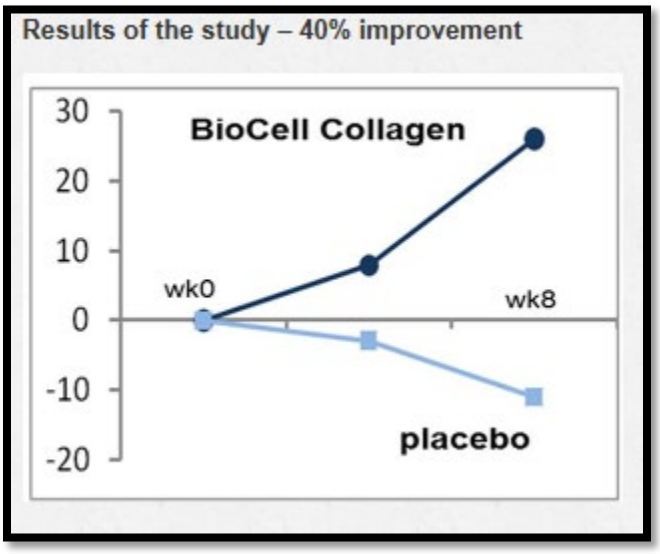


Figure 9 - Compared to placebo, after eight weeks the intervention group significantly reduced joint discomfort by as much as 40%.[94]

*The WOMAC (Western Ontario and McMaster Universities) index is used to assess patients with degeneration of the hip or knee using 24 parameters. It can be used to monitor the course of the problems/pain/function or to determine the effectiveness of anti-rheumatic therapies.
**VAS: Visual analogue score for pain

In another double-blind placebo-controlled study published in 2012, researchers divided healthy subjects with joint pain into two groups and administered either two grams of BCC or placebo for 70 days. Outcome measurements included the same VAS for pain and WOMAC scores taken on days 1, 35, and 70. The tolerability profile of the treatment group was comparable to that of the placebo. The results, depicted in Figure 10, demonstrated that the treatment group, as compared to placebo, had a significant reduction of VAS pain on day 70 and of WOMAC scores on both days 35 and 70. The BCC group experienced a significant improvement in physical activities compared to the placebo group on days 35 and 70. BCC was well tolerated and found to be effective in managing damaged joint associated symptoms over the study period, thereby improving subjects' activities of daily living.[37] Further, as displayed in Figure 11 the authors determined that 71% of all subjects experienced a minimum of 30% less discomfort (not to be confused with 30 mm*).[37]

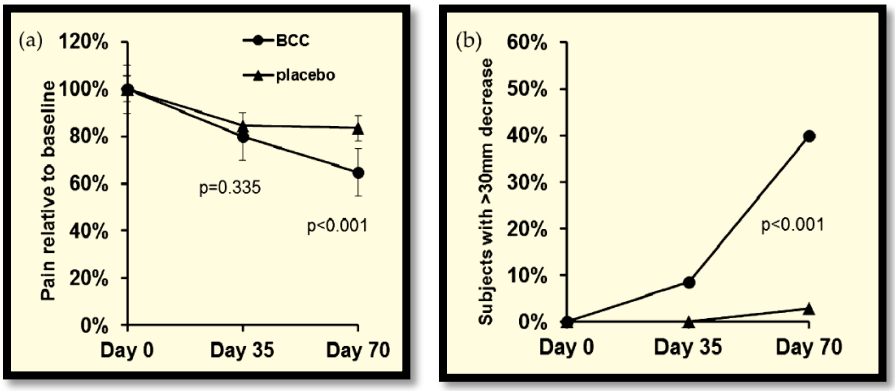


Figure 10 - Effect of daily supplementation with BCC on VAS pain score compared to placebo: (a) baseline-adjusted VAS scores on days 35 and 70 in each treatment group; (b) comparison of the percentage of subjects in each treatment group who experienced a decrease in VAS pain score by at least 30 mm* on days 35 and 70, as compared to the baseline score on day 0.[37]

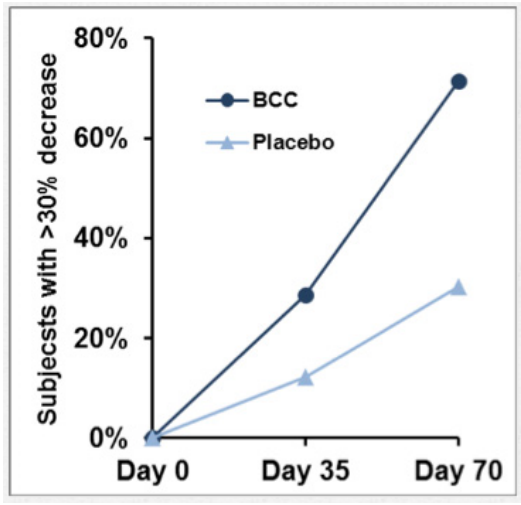


Figure 11 - Results of study showed a minimum of 30% less discomfort in 71% of subjects taking BCC[37]

** A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. An example of a VAS would be a numeric scale of 1 to 10 to represent severity of pain (1 being little to no pain and 10 representing excruciating pain).*100-mm VAS. Ratings of 0 to 4 mm can be considered no pain; 5 to 44 mm, mild pain; 45 to 74 mm, moderate pain; and 75 to 100 mm, severe pain.

In a pilot randomized controlled sports nutrition study, Lopez et al. researched the potential effect of BCC on biomarkers and functional indices of recovery from intense exercise.[9] In an RCT using trained healthy individuals performing muscle-damaging upper body exercise and 3 g/day of BCC versus placebo, the treatment group had beneficial effects on connective tissue protection and recovery. Besides significantly better biomarker measurements (BCC further attenuated biochemical markers of skeletal muscle tissue damage compared to placebo), the authors also found that the overall trend for the performance decrement (see Figure 12), together with the results for the perceived recovery scale, suggested a more robust muscular recovery and adaptive response occurred in the BCC group.[9]

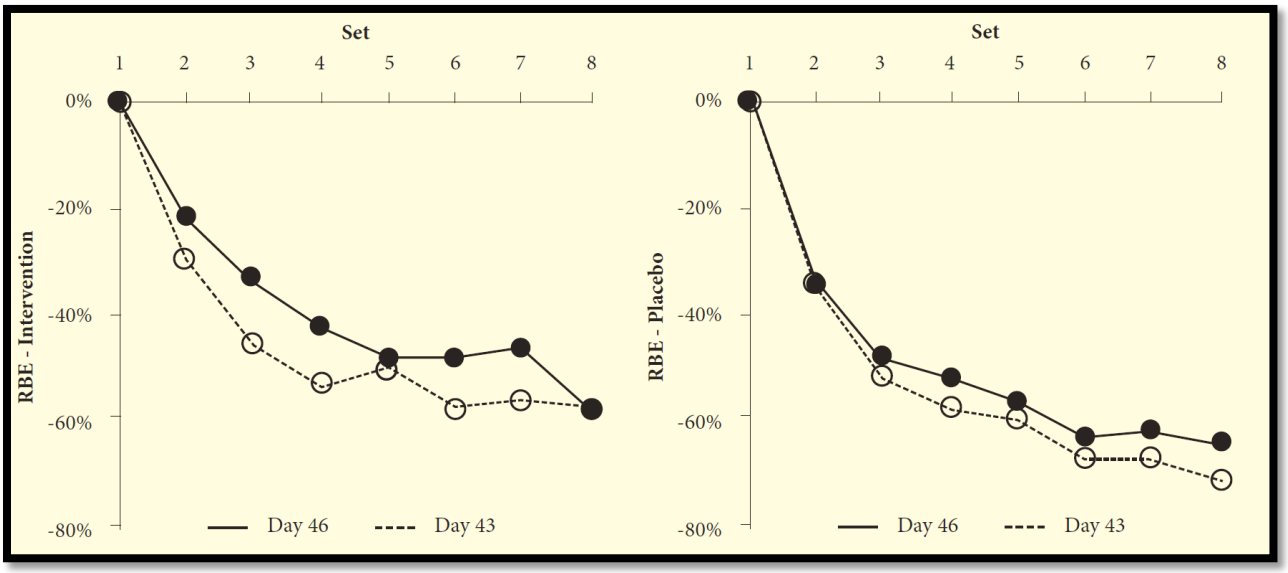


Figure 12. Left pane shows the repetitive bout effect in the BCC subjects; right pane shows it for the placebo group. The solid line represents the performance decrement on day 46. The dotted line represents the same on day 43. [9]

Other studies using like-ingredients/formulation have had similar results[6,102,103]

Background – Collagen, Hyaluronic acid (HA), Chondroitin Sulfate (CS) and Extracellular Matrix (ECM) in Skin

Collagen and related GAGs, responsible for skin health, decrease with age and compromised by environmental insults such as photodamage, which can be attenuated through proper supplementation

Please see previous section for individual details and mechanisms of action, as they are fundamentally the same in collagenous tissues (e.g., skin, hair, joint/connective tissues, bone, etc.) especially as it relates to ECM homeostasis.

Skin Aging

The ECM is the largest component of normal skin, and like joints, it gives the skin its unique properties of elasticity, tensile strength, and compressibility.[104,105,106] Therefore, (along with photodamage) the aging process effects skin elasticity and structure in a similar manner as other collagenous tissues throughout the body such as joints (see ECM section above), as collagen and elastin lose function contributing to a loss of skin tone and outward signs of aging (e.g. wrinkles, reduced epidermal thickness, dryness, etc.).[107,108] Another sign of skin aging is the loss of moisture, which is partially caused by a natural and/or environmentally accelerated reduction of HA, which can absorb up to 1,000 times its weight in water, explaining how a reduction in this skin GAG leads

to related aging signs.[109,110] Both intrinsic (chronological aging) and extrinsic (environmental, which causes the majority damage as humans age) factors of skin aging possesses unique etiologies, but they share much of the same physiological mechanisms associated with their development.[111]

Photoaging

Along with the loss of collagen in aging, as Figure 13 portrays, environmental exposures (e.g., diet, stress, pollution, sun, etc.) accelerate the skin aging process by reducing cellular metabolism including natural physiological responses, increasing free radical production while lessening an adequate antioxidant response, and causing the degradation of collagen. The primary extrinsic factor leading to accelerated skin aging is photodamage (AKA photoaging).[112,113] UV radiation increases the formation of free radicals in the skin, causing DNA damage and expression of matrix metalloproteinases (MMPs) responsible for the degradation of extracellular matrix proteins such as collagen, elastin, and hyaluronic acid (also see Figure 3A & 3B above).[114,115,116] All these changes reflect on the skin, manifesting as skin dryness, changes in elasticity, and appearance of wrinkles and contribute to premature skin aging. Further, environmental insults, especially photodamage, cause the majority of visible aging signs and are therefore largely preventable.

Figure 13A - Environmental insults including Pollution, UV exposure, stress, etc.

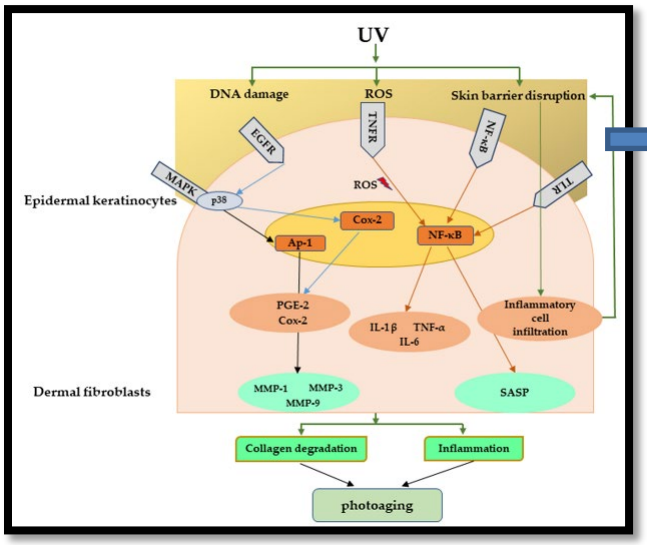
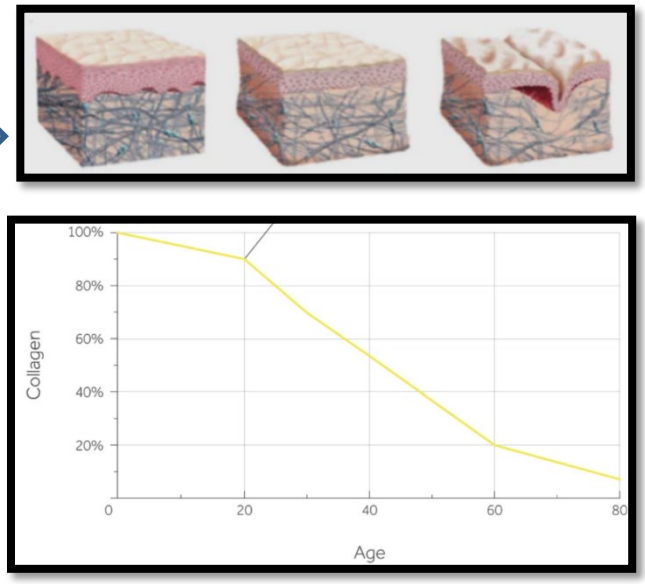


Figure 13B - Projected skin appearance over time based on extrinsic (environment) and intrinsic (chronologic) aging



Figures 13A and B depict structural changes in skin ECM (dermis) and outward results (epidermis) over time from both intrinsic (chronological aging) and extrinsic (environmental) factors. The figures portray the natural age-related decline in the body's collagen production (graph) combining with environmental insults (left pane) in compromising skin ECM leading to the projected cumulative visible result (upper right).

Oral Skin Treatments

Addressing the intrinsic and extrinsic factors leading to visible signs of aging skin depicted above, oral (and topical) treatments have been used to improve skin conditions by supplying active ingredients for the skin ECM structure and function, skin hydration and protection as well as for the improvement of cutaneous changes

caused by photoaging.[42,117,118] Further, specialized hydrolyzed collagen containing supplements administered orally have been shown to stimulate dermal fibroblasts, PGs, increase collagen synthesis and elastin, thus slowing the physiological decline of dermal tissue with improvements in ECM synthesis and enhancements in fibroblast growth.[95,119,120,121,122,123,124]

Therefore, properly hydrolyzed collagen peptides combined with glycosaminoglycans (e.g., CS, HA, etc.), such as BCC,[5,90,95] are commonly used for skin protection, restoration and overall health.[91,92,117,118,124,125,126,127] Further, oral supplementation with collagen peptides have shown greater effects on skin compared to topical products,[117] or what is often referred to as "beauty from within," especially when combined with certain vitamins, minerals and other non-vitamin/mineral antioxidants such as carotenoids.[117,125,126,128,129,130,131,132,133]

BCC in Skin Health

Supplementation with BCC has demonstrated efficacy in addressing both extrinsic (environmental) and intrinsic (chronological) skin aging factors.

Swartz and Park et al. in a pilot study published in the Journal of Clinical Interventions in Aging, had 26 healthy females who displayed visible signs of natural and photoaging, ingest supplementation of 1 gram daily of BCC for 12 weeks. After 12 weeks, the subjects showed a significant reduction of skin dryness/scaling (76%) and global lines/wrinkles (13.2%) as measured by visual/tactile score.[95] Additionally, a significant increase in hemoglobin (17.7%) and collagen (6.3%) in the skin dermis was found after 6 weeks of supplementation. At 12 weeks, the increase in hemoglobin remained significant (15%), and the increase in collagen content was maintained, but the difference from baseline was not significant (3.5%). Figure 14 shows the outward results of 1 g/d of BCC on the reduction of facial aging signs.[95]

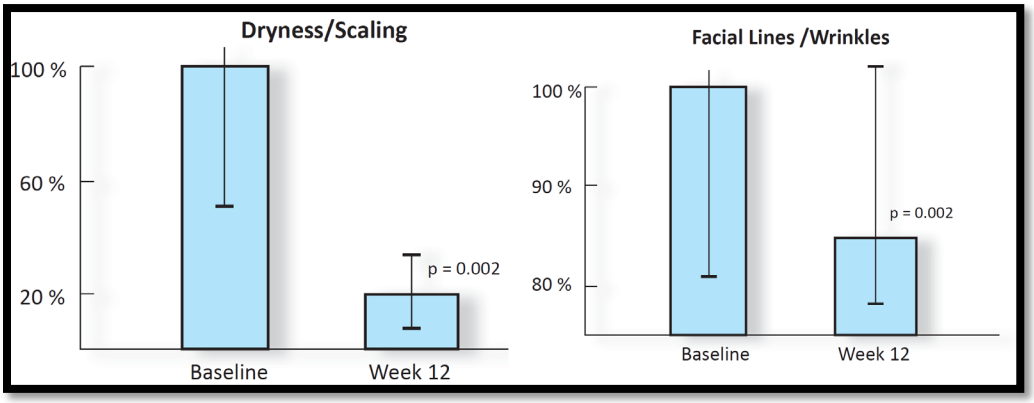


Figure 14 - The reduction of facial aging signs from 12 weeks of BCC ingestion[95]

Study results and potential mechanisms:[95]

1. **Reduction of wrinkles and fine lines** (measurement using visual/tactile scores). Ingredients help push skin ECM towards homeostasis and help protect against photodamage.
2. **Improvement of skin texture by increasing hydration** (relative degree of skin hydration was assessed using the dermal phase meter [DPM] 9003) **and reducing skin scaling.** A majority of the study subjects enjoyed remarkable improvement of their skin tone as measured using visual/tactile scores.
3. **Maintenance of the integrity and healthy level of HA.** HA plays an essential role in skin hydration by retaining water in the dermis. BCC helps maintain healthy levels of HA not only by elevating HA levels about 60-fold in the bloodstream (see Figure 7 above) but also by inhibiting HA degradation.

4. **Increase in collagen content** (measured by Cosmetrics™ SIAscope*)**.** The aging process leads to the loss of dermal collagen, which is the key factor of wrinkle generation. BioCell Collagen antagonizes it and increases collagen content in the dermis.
5. **Enhancement of blood microcirculation in the face** (measured by SIAscope*). Various cells reside in the skin including dermal fibroblasts which produce collagen, elastin, HA, and other ground substances that fill the skin layer. Improved blood microcirculation effectively nourishes the cells with oxygen and nutrients while removing wastes from the tissue.

*The SIAscope measures structural molecule content in the dermis and is used to evaluate how the metabolism of key molecules in the skin such as collagen and melanin were affected by BCC supplementation.

The success of the Swartz et al. BCC pilot study described above, led to the recent randomized, double-blind, placebo-controlled clinical trial (RCT) that showed 1 g/d of BCC delivered measurable improvements in signs of skin aging in women, represented by increased skin elasticity, reduction of crow's feet, and improvement in depth and number of fine lines and wrinkles.[5] Consistent with the BCC pilot study and others cited throughout this paper, the researchers found a statistically significant increase in the subject's dermal collagen. 86.2% of the 113 subjects who completed the study had an increase in cutaneous collagen content by 12%. The complete results are listed below and graphed in Figures 15 A-D.

- Significantly reduced facial lines and wrinkles (P = .019) and crow's feet lines and wrinkles (P = .05)
- Increased skin elasticity (P = .008) and cutaneous collagen content (P < .001) by 12%
- Improved indicators associated with a more youthful skin appearance based on visual grading and wrinkle width (P = .046)
- Decreased skin dryness and erythema (reddening of the skin)

Interestingly, both groups decreased skin dryness, but there was no difference between the supplement and the placebo in skin surface water content or retention, suggesting a longer period may be necessary to quantify improvements in these two conditions. To be sure, HA has a relatively short half-life in the blood (~3-5 minutes) and less than a day in the skin,[134] therefore it has been proposed that more frequent dosing may help keep HA levels consistently higher in the skin.[5,124] The final authors' conclusion is as follows: "Dietary supplementation with chicken, sternal cartilage extract supports the accumulation of types-I/III collagen in skin to promote increased elasticity and reduced skin wrinkling."[5]

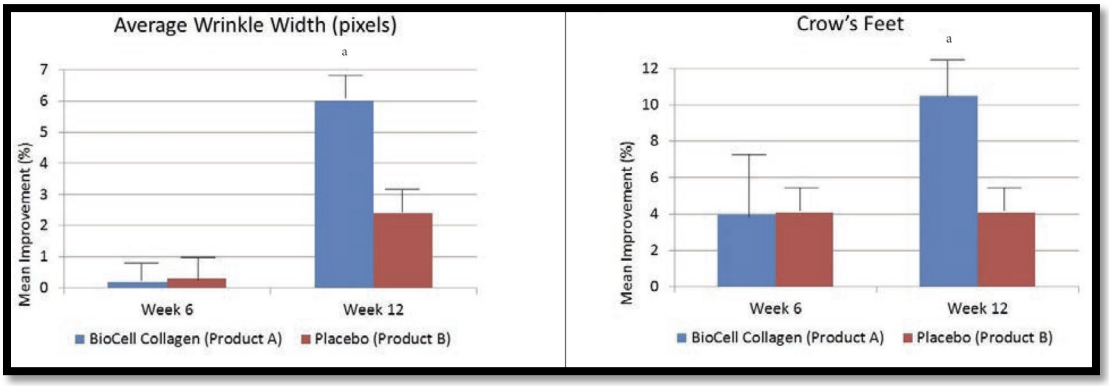


Figure 15A - Average wrinkle width - mean percentage change from baseline for a 46-year-old female. The data were obtained using Clarity photography image analysis

Figure 15B - Crow's feet wrinkles: Mean percentage change from baseline for a 58-yr old female. The data were obtained using expert visual grading.

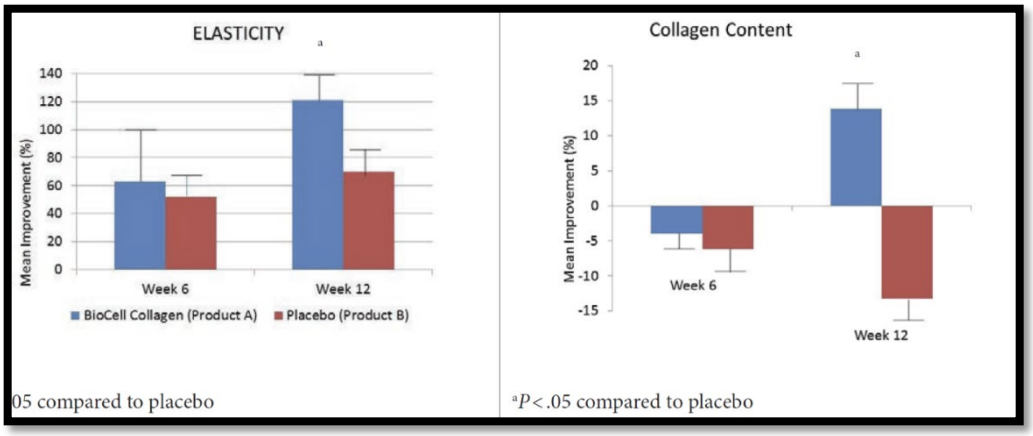


Figure 15C - Skin elasticity, mean percentage change from baseline using the Cutometer bioinstrumentation data (RO)

Figure 15D - Mean percentage change in collagen content from baseline. The data were obtained using the Siascope bioinstrumentation.

Figures 15 A-D - The results of 12 weeks of daily supplementation with the intervention reducing visible and measurable, age-dependent signs on the face, including (A) depth of wrinkles, (B) crow's feet lines, and (C) elasticity; (D) 86.2% of women in BCC group showed improvement in collagen levels at 12 weeks compared to baseline compared to only 7.3% in the placebo group. [5]

Seeking BCCs Mechanisms of Action in Skin Protection and Health

As noted, extrinsic skin aging is primarily caused by chronic UV exposure and characterized as photoaging.[111] Effects of collagen supplementation on photoaging has mostly focused on type I collagen, since it is the primary collagen in human skin.[135] However, the previous BCC skin studies (and other studies using supplements containing predominately type II collagen) discussed here have proven successful in improving visible signs of aging skin. Therefore, Phipps et al. performed research to see how these other types of collagens also have protective photoaging properties.[90] Researchers used BCC for 14 weeks in hairless mice under continuous UV exposure (UVB-irradiation) to rapidly induce skin related aging damage commonly associating with human photoaging such as reduction in skin elasticity and HA content; increases in matrix metalloproteinase (MMP) expression (MMP -enzymes responsible in degrading ECM components), dermal inflammatory cells, transdermal water loss (TDWL), collagen fiber occupied regions and wrinkles (see Figure 13A).[90] In the treatment group, compared to the control animals, all skin-related (photoaging) parameters measured in the study were statistically significantly better suggesting a large photoaging protective effect. The author's conclusion is as follows: "14 weeks of BCC supplementation improved several signs of UVB-induced photoaging in hairless mice (increases in skin elasticity and hyaluronic acid content, as well as reductions in MMP expression, TDWL, dermal inflammatory cells, collagen fiber occupied regions and the number, area, length and depth of wrinkles), compared with UVB-exposed vehicle controls." These results were likely because the supplement's size (smaller hydrolyzed collagen peptides[136]) and synergy of the natural occurring components of this novel hydrolyzed chicken sternal cartilage extract (see Figure 6 and 16) demonstrating its benefit as a functional ingredient for the improvement of skin health.[90,96] For complete results from this study, including related measurement statistics used to determine BCC's potential mechanism of actions in protecting skin from damaging effects of photoaging, readers are referred to the published data by Phipps et al. in the Journal of Functional Foods. Further, in 2010, BioCell Technology LLC, received Generally Recognized As Safe (GRAS) approval by an independent expert panel for its patented, clinically substantiated ingredient, BioCell Collagen II®.

Summary

Intrinsic (chronological aging) and extrinsic (environmental including lifestyle/activities) factors weaken our connective tissues, such as joints, skin, tendons and ligaments as we age through decreasing the production and/or acquisition of the molecules that make up these tissues. In other words, as with most physiological aging aspects, connective tissue homeostasis is compromised as degradation surpasses synthesis and environmental insults compound overtime. Therefore, supplementing to support the structure, function, health and longevity of these critical tissues has become commonplace. However, the efficacy of collagen supplementation in regard to supporting protection or the health of connective/collagenous tissues, such as joints, skin, tendons and ligaments, which are primarily composed of an extracellular matrix (ECM), has been shown to be dependent on the size and makeup of the ingested compound. Properly sized hydrolyzed collagen and other ECM supporting molecules such as chondroitin sulfate and hyaluronic acid in a naturally occurring synergistic form that closely mimics the composition of the human ECM for joints and skin (see Figure 16), have shown significant and consistent success in reaching the target tissues and delivering the desired results of protecting skin and joint health including improving signs of aging skin, joint mobility and alleviating minor joint discomfort. BCC's patented extraction and manufacturing procedure remarkably reduces the size of all its biomolecules making them highly absorbable and available to the target tissues. And the natural synergy of the bio-actives makes them functional in the target tissues (connective tissues, especially joint and skin ECM).

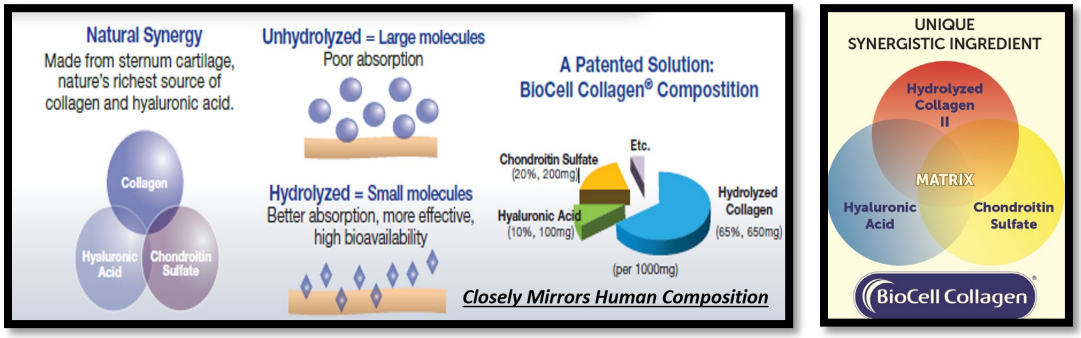


Figure 16 - Patented process delivers natural ingredient synergy/ratio mimicking human molecular composition and reduces molecule size for proper absorption and action at target tissues.[96]

Seven clinical trials support BCC's patented cartilage extract, arriving at target tissues (skin and joint) as they demonstrated safety and efficacy in the following areas:

- **Joints:** improvement, protection, and maintenance of the overall health of joints/connective tissues including during exercise and aging
  - Mitigating minor joint discomfort; improved mobility and physical activities
  - Safe alternative to non-steroidal anti-inflammatory drugs (NSAIDs), and their well-known side effects, for mild to moderate joint discomfort
  - Athletes/exercisers for joint recovery from specific activities that severely challenge connective tissues (e.g., jumping, fast direction changes, etc.) by supporting musculoskeletal tissue remodeling including enhancing cartilage synthesis to also help attenuate performance decrements possibly reducing risk of injuries
- **Skin:** improved overall skin health
  - Protection from photoaging including helping maintain the integrity of the ECM in the dermis below the skin, crucial for youthful skin appearance
  - Enhanced collagen content, blood microcirculation and reduced facial aging signs including reduced wrinkles, improved skin tone, improved hydration, smoother and more supple skin

Unique Features

- Incorporates BioCell Collagen II: micronized (low molecular weight) hydrolyzed collagen peptides and glycosaminoglycans (GAGs) derived from cartilage ECM that include a naturally occurring matrix of collagen type-II peptides, HA, and CS (i.e., from a single naturally occurring source, rather than unnatural percentages/ratios from single sources), allows the bio-active ingredients passage to, and activity in, target tissues
- Seven clinical trials support the safety and efficacy of BCC's patented extract in support of joint and skin restoration and health.
- 2 in 1 product: may be the best non-medical solution for joint and skin health
- Manufactured in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC
- NSF Certified for Sport
- Formula considers use of other dotFIT products to help the user maintain a safe and optimal range of total nutrient/supplement intake

Typical Use

- Individuals concerned with joint/cartilage health to improve mobility, joint comfort, knee-joint strength and specifically designed for overuse or age-related joint discomfort
- Recovery from specific activities that severely challenge connective tissues (e.g., jumping, fast direction changes, etc.) and attenuate performance decrements thus possibly reducing risk of injury
- Individuals seeking to maintain or improve skin health and appearance, by offering protection from normal aging factors that lead to visual signs of skin aging, thus supporting a more youthful skin appearance
- To support youthful skin and joint health, to help off-set the age-related decline, take one (1) capsule in the morning and one (1) capsule at night starting at approximately 35 years of age
- Adults supporting skin health only, take one (1) capsule daily
- Adult athletes seeking faster connective tissue recovery from activities may start at any age taking one (1) capsule in the morning and one (1) capsule at night. for optimal results, take two (2) capsules in the morning and two (2) capsules at night during intense training cycles, injury recovery, or as directed by your health care professional

Adverse events, precautions, or contraindications with BioCell Collagen, the only ingredient/compound in JointFlexPlus, are rare or unknown in healthy people supplementing the diet properly as described above. The section below is a summary related to specific sub-populations. Qualified practitioners needing more information are referred to the TRC Natural Medicine Data Base which is continually updated with emerging evidence-based data.[137]

Precautions

The ingredient/compound in the JFP are considered to be safe at the recommended dose.[5,9,37,90,93,94,95,96]

Contraindications

The use of JFP is not recommended during pregnancy or lactation due to the absence of data for these populations. No known contraindications exist at this time.

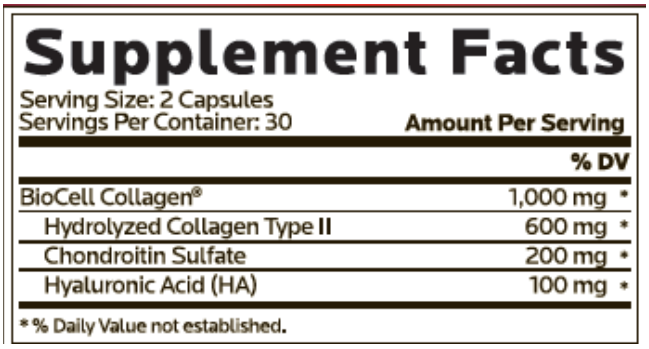
Adverse Reactions

Study participants who used 1,000 mg of BioCell Collagen twice daily for two months experienced the same adverse events as the placebo group and were insignificant and not related to the study substances. [5,9,37,93,94,95] No adverse events for the compound has been reported in literature.

Upper Limit/Toxicity

There are no known overdoses of the BioCell Collagen ingredients either individually or as the formula.[137]

Supplement Facts Panel



Supplement Facts

Serving Size: 2 Capsules
Servings Per Container: 30

	Amount Per Serving	% DV
BioCell Collagen®	1,000 mg	*
Hydrolyzed Collagen Type II	600 mg	*
Chondroitin Sulfate	200 mg	*
Hyaluronic Acid (HA)	100 mg	*

* % Daily Value not established.

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