REFERENCE SHEET:

Collagen

Pronunciation

Collagen (kaw-lah-jen)

Summary

Collagen is found throughout the body in connective and fibrous tissues including skin, bone, cartilage, tendons, ligaments, intervertebral discs, hair, cornea, blood vessels, and the reticular fibers of most organs. Collagen is built from peptide chains consisting of glycine and a combination of other amino acids, most commonly proline and hydroxyproline. Approximately 28 different kinds of collagens exist, but five of the most common types include type I (dermis, tendons, ligaments, bone), type II (cartilage, vitreous body, nucleus pulposus), type III (skin, vessel wall, reticular fibres), type IV (basal lamina, epithelial layer of basement membranes), and type V (lung, cornea, hair, fetal membranes, bones). Type X collagen may have a role in bone health, particularly through the mineralization of cartilage in the subchondral bone. Supplements may contain collagen derived from bovine, porcine, marine and other sources, such as eggshell membranes.

Main Medical Uses

Evidence supports the use of collagen in treating conditions involving joint pain, including osteoarthritis, activity-related joint pain, and rheumatoid arthritis. It may be used in treating or preventing exercise-induced injury, osteoporosis, type II diabetes, and hypertension. Evidence also supports its use to treat brittle nail syndrome and a number of dermatological applications, including pressure ulcers, edematous fibrosclerotic panniculopathy (cellulite), and skin aging.

Dosing and Administration

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Skin Aging	1.0-10g per day (fish-derived Type I hydrolyzed collagen) for 4-12 weeks	↓ dry skin, wrinkles, nasolabial fold depth; ↑ collagen density, skin firmness, elasticity & dose-dependent moisture of stratum corneum	B	↑ collagen density, collagen fragment size, glycosaminoglycan level & collagen content; ↓ collagen fragmentation
	2.5- 5.0g per day (porcine-derived Type I collagen hydrolysate, Verisol®) for 8 weeks, or 10g for 4 weeks	↑ skin elasticity (greatest effect on ages > 50 in low doses), moisture of stratum corneum (greatest effect on ages > 30)	B	↑ collagen & elastin synthesis ↑ skin moisture, elasticity, & pliability; ↓ sebum content
	10g per day (fish-derived collagen peptides, Peptan®) for 8 weeks	↑ collagen density, collagen fragment size, skin moisture (12%); ↓ collagen fragmentation	B	
	2.5-10g per day (porcine-derived collagen peptides, Verisol® Type I collagen; Peptan®) for 8 weeks	↑ skin moisture (28%), procollagen type I & elastin content by 65% & 18%, respectively; ↓ eye wrinkle volume by 20%, and by 11.5% 4 weeks after end of treatment	B/C	
Cellulite	2.5g per day (porcine-derived collagen peptides, Type I collagen, Verisol®) for 6 months	↓ degree of cellulite and skin waviness; ↑ dermal density. Effects observed to a greater extent in subjects with normal BMI compared with higher BMI.	B	↓ fat cells and lymphatic fluid between dermis and subcutis causing a decrease in borderline length between dermis and subcutis

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Pressure Ulcers	15g three times per day (collagen hydrolysate) for 8 weeks	↑ ulcer healing as measured by PUSH tool scores	B	↑ recruitment & stimulation of immune cells & fibroblasts; spares extracellular matrix components structure through its own degradation by matrix metalloproteinases
Hypertension	2.9g per day (chicken-derived collagen hydrolysate) for 12 weeks	↓ systolic BP, trending decrease in diastolic BP, brachial-ankle pulse wave velocity; ↑ serum NO	B	↑ serum NO ↓ plasma renin; ↑ endothelial progenitor cell colonies ↓ ACE activity
Type II Diabetes	6.5g twice per day (as marine collagen peptides) for 3 months	↓ FBG, GHbA1C, fasting blood insulin, total TGs, total cholesterol, LDL & free fatty acids, hs-CRP, NO, resistin, prostacyclin, leptin & CYP450; ↑ insulin sensitivity, HDL, bradykinin, PGI2 & adiponectin	B	↓ FBG, GHbA1C, fasting blood insulin, total TGs, total cholesterol, LDL & free fatty acids, hs-CRP, NO, resistin, prostacyclin, leptin & CYP450; ↑ insulin sensitivity, HDL, bradykinin, PGI2 & adiponectin
Osteoarthritis	40g per day (chicken-derived cartilage, undenatured Type II collagen, UC-II®) for 180 days	↓ overall WOMAC score, & subscales for pain, stiffness & physical function in the knee	B	↓ CTX-II (57), TNF-α ↑ cartilage area, chondrocytes, & proteoglycan matrix; ↓ MMP13 protein & apoptosis, synovial hyperplasia, TNF mRNA ↓ inflammatory cells, edema, CD3 & CD20 lymphocytes, CD68 macrophages, MMP2, IL1 β , TNFα, IL17, IL10, & type V collagen; ↑ thick & thin collagen, type I collagen, caspase 9 in the synovial membrane ↑ extracellular matrix macromolecule synthesis by chondrocytes
	10g per day (collagen hydrolysate) for 6 months	↓ knee joint discomfort via VAS & WOMAC scales	B	
	2g per day (chicken-derived hydrolyzed collagen Type II, BioCell®) for 70 days	↓ VAS pain & WOMAC scores, & difficulty of physical activity	B	
	500mg per day (eggshell membrane derived, NEM®) for 8 weeks	↓ knee pain and stiffness	B	

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Rheumatoid Arthritis	0.1mg per day for 1 month, then 0.5mg for 2 months (chicken-derived Type II hydrolyzed collagen)	↓ swollen and tender joint frequency	B	↓ rheumatoid factor, TNFα ↓ CTX-II ↓ inflammatory cells, edema, CD3 & CD20 lymphocytes, CD68 macrophages, MMP2, IL1 β , TNFα, IL17, IL10, & type V collagen; ↑ thick & thin collagen, type I collagen, caspase 9 in the synovial membrane ↓ total IgG anti-collagen II antibodies
	0.1mg per day (chicken-derived Type II collagen) for 24 weeks	↓ pain, morning stiffness duration, tender & swollen joint count, HAQ & efficacy scores. 68.57% & 40.95% patients met ACR20 & ACR50 criteria. MTX more effective in all measures, but had more adverse events	B	
	0.1mg per day (chicken-derived Type II collagen) for 24 weeks	All results same as above but 41.55% & 16.89% patients met ACR20 & ACR50 criteria.	B	
	0.02mg, 0.1mg, 0.5mg, or 2.5mg per day (chicken-derived Type II collagen) for 24 weeks. Patients allowed to maintain NSAID/steroid usage	↓ paulus criteria with 0.02mg, with trend of decreasing scores with higher doses for Paulus & ACR criteria, & swollen/tender joints	B	
	0.05, 0.5 or 5mg (bovine-derived Type II collagen)	↓ total IgG anti-collagen II antibodies. Best clinical response in IgG2 and IgG3 by 0.5mg	B	
Injury Prevention/ Tissue Repair	5 or 15g gelatin (enriched with 48mg vitamin C) three times per day, 1-hour before exercise for three days	↑ serum glycine, proline, hydroxyproline, and hydroxylysine (1-hour peak). 15g doubled collagen I propeptide. ↑ collagen and mechanics in blood-treated ligaments	C	↑ serum glycine, proline, hydroxyproline, and hydroxylysine, collagen I propeptide (↑ collagen synthesis)

Condition	Dosing & Administration	Outcome	Class of Evidence	MOA
Joint Pain & Exercise Induced Joint Pain	40mg per day (chicken-derived undenatured type II collagen, UC-II®) for 120 days	↑ knee extension compared to placebo & baseline, exercise time before joint pain	B	↓ CTX-II ↑ cartilage area, chondrocytes, & proteoglycan matrix; ↓ MMP13 protein & apoptosis, synovial hyperplasia, TNF mRNA ↓ inflammatory cells, edema, CD3 & CD20 lymphocytes, CD68 macrophages, MMP2, IL1 β , TNFα, IL17, IL10, & type V collagen; ↑ thick & thin collagen, type I collagen, caspase 9 in the synovial membrane
	10g per day (collagen hydrolysate, CH-alpha®) for 24 weeks	↓ joint pain while resting, walking, standing, carrying objects, & lifting. Effect greater in patients with arthralgia who also had less pain while running and changing direction	B	
	1.2g per day (bovine-derived collagen hydrolysate, AminoLock®) for 6 months	↓ pain via VAS score	B	
	5g per day (collagen peptides, Fortigel®) for 12 weeks	↓ activity-related pain intensity	B	
	500mg per day (eggshell membrane-derived, NEM®) for 2 weeks	↓ the biomarker C-terminal cross-linked telopeptide of type-II collagen (CTX-II), immediate stiffness, recovery pain & stiffness	B	
Tendinopathy	2.5g twice per day (hydrolyzed collagen peptides, Tendoforte®) for 3 months	↑ VISA-A score; ↓ microvascularity	C	↓ microvascularity ↓ IL-1 β -induced NF- κ B activity, p65 nuclear translocation, COX-2, MMP-1, caspase-3; ↑ collagen type I & β 1-integrin receptor expression
Osteoporosis Prevention	5.0g per day (collagen peptides, Fortibone®) for 12 months	↑ spine and neck bone mineral density, N-terminal propeptide of type I collagen (P1NP)	B	↑ BMD, P1NP ↑ MC3T3-EI pre-osteoblastic cells, alkaline phosphatase, osteocalcin, runx2

For an explanation of the classes of evidence, please see the Rating Scales for Evidence-Based Decision Support.

Forms

Collagen is extracted from the skins, bones, cartilage, and tendons of animal sources using hot water (e.g. above 40 degrees Celcius), creating gelatin. Enzymes can hydrolyze gelatin into collagen hydrolysate which is the main form of collagen used in dietary supplements. Gelatin is derived from denatured and partially hydrolyzed collagen and has a molecular weight of 100kDa. It can be further refined by proteinases into collagen peptides with molecular weights between 0.3-8kDa. The lower molecular weight of hydrolyzed collagen ultimately provides advantages in absorption and distribution compared to native collagen.

Collagen is made up of several amino acids, which may affect its absorption and bioactivity. Hydrolysates consist primarily of glycine (GLY), proline (PRO), hydroxyproline (HYP), glutamic acid (GLU), arginine (ARG), alanine (ALA), as well as other essential and non-essential amino acids, such as aspartic acid (ASP), threonine (THR), serine (SER), cysteine (CYS), valine (VAL), methionine (MET), isoleucine (ILE), leucine (LEU), tyrosine (TYR), phenylalanine (PHE), lysine (LYS), and histidine (HIS).

Form	Source	Bioavailability
Collagen Hydrolysate	Silver carp skin	Dose-dependent increase in HYP with lower molecular weight showing the greatest effect compared to higher weight and gelatin
	Chicken	ALA-HYP max concentration (human): 2.27 nmol/ml
	Porcine skin	ALA-HYP max concentration (human): 26.01 nmol/ml GLY-PRO-HYP max concentration (human): 21.13 nmol/ml PRO-HYP max concentration (human): 16.84 nmol/ml GLY-PRO-HYP max concentration (rat): 130 nmol/ml
Gelatin Hydrolysate	Fish scale vs. porcine skin	Type I collagen types: Fish scale gelatin hydrolysates significantly higher free form Hyp AUC than porcine skin
	Fish scale	PRO-HYP max concentration (human): 60.65 nmol/ml, 163 nmol/ml PRO-HYP and HYP-GLY max concentration (human): 120 nmol/ml PRO-HYP-GLY max concentration (human): 0.663 nmol/ml
	Porcine skin	HYP-GLY max concentration (human): 4.2 nmol/ml
	Bovine skin	ALA-HYP-GLY max concentration (rats): 0.78 nmol/ml
	Gelatin	Relative and absolute bioavailability was 74.12% & 85.97%, respectively in rats
Non-hydrolyzed Collagen	Bovine hide	Lesser GI transport efficiency and digestion than hydrolyzed collagen due to lower molecular weight in vitro

Pharmacokinetics

Absorption

Similarly to other proteins, collagen hydrolysates are degraded in the digestive tract and are mostly absorbed as amino acids, dipeptides, and tripeptides via the brush-border membrane using the H+-coupled peptide transporter, PEPT1. Subsequently, they enter the bloodstream by crossing the basolateral membrane. Ingestion in tripeptide form may improve absorption efficiency in humans.

Distribution

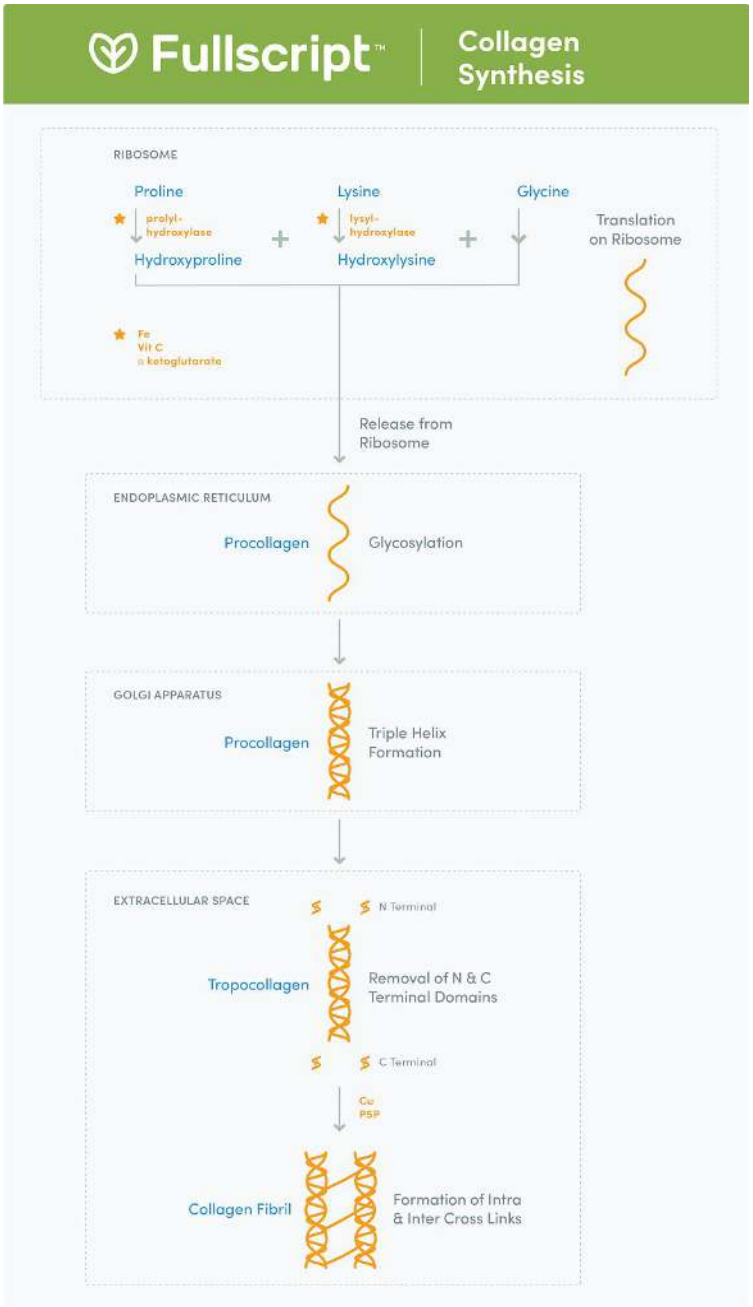
The collagen hydrolysate peptide, PRO-HYP, has been shown to be distributed to the skin, cartilage, and bone marrow in its intact form, with its highest concentration in gastric and intestinal walls.

Metabolism

The liver metabolizes collagen peptides, though many HYP-containing peptides (some of which can be larger than tripeptides) can pass through the liver to enter systemic circulation.

Excretion

If not reabsorbed by PEPT1 and PEPT2, collagen hydrolysate peptides can be excreted in the urine after ingestion.



Adverse Effects

Collagen supplements are generally considered as safe without the common occurrence of adverse effects. Feelings of fullness or disagreeable taste have been reported in rare cases. To avoid the possibility of allergic reactions, consideration of the source of collagen may be required.

Associated Depletions and Interactions

Despite evidence for the effectiveness of collagen supplementation in rheumatoid arthritis, some trials report no effect of bovine Type II supplementation in rheumatoid arthritis when added to existing medication (i.e.. methotrexate, hydroxychloroquine, gold sodium thio-glucose or gold sodium thiomalate, sulfasalazine, azathioprine, auranofin, D-penicillamine, or prednisone). Additionally, chicken-derived Type II collagen supplementation may not maintain methotrexate's anti-inflammatory effects, though it may induce fewer adverse events.