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A Comprehensive Review on the Role of Collagen in Health and Disease

Nipun Saravanan Pillai, Sara Anees Khan*, Nupur Mehrotra and Kaustubh Jadhav

Department of Biochemistry, SVKM's Mithibai College of Arts, Chauhan Institute of Science & Amrutben Jivanlal College of Commerce and Economics (EMPOWERED AUTONOMOUS) Affiliated to University of Mumbai, India.

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The most prevalent protein in the human body, collagen is essential for preserving the structural soundness and functionality of different tissues. It is an essential part of connective tissues, which include skin, cartilage, bones, tendons, and ligaments. It also plays a key role in wound healing, cell signaling, and tissue repair. The many functions of collagen in human health and its connections to different illnesses are examined in this overview. It looks at the biochemical and structural characteristics of the many forms of collagen, the processes by which collagen is synthesized and broken down, and how imbalances can result in diseases including cardiovascular problems, fibrosis, osteoarthritis, and skin aging. There is also discussion of new treatment options, such as supplements, collagen-based biomaterials, and regenerative medicine techniques. New treatments targeted at promoting tissue repair, boosting quality of life, and avoiding collagen-related illnesses may be made possible by a better understanding of the many roles that collagen plays in both health and disease.

Keywords: Collagen, Joint health, Skin elasticity, Wound healing, Therapeutic applications**.**

About Collagen

The most prevalent extracellular matrix protein, collagen. The molecular framework of collagen is like that of a rope. Triple helixes are created when three chains wind around one another in order to form collagen. These constituents unite to generate collagen fibrils with remarkable strength and tensile force [1,2,3]. Amino acid-based protein molecules make up collagen. It gives the extracellular matrix, or framework, of connective tissue structural support. It is the perfect matrix for bones, tendons, ligaments, and skin because of its rigidity and resistance to stretching [4]. Collagen is found in many different types of living organisms and serves primarily as a linkage between tissues in biotic systems. Moreover, the protein that is most prevalent inside the extracellular matrix (ECM). Extracellular matrix (ECM), a non-cellular protein prevalent in each and every organ and tissue, serves as a structural truss to regulate cellular growth, metabolism, adhesion, and migration [5].

Based on the kinds of structures they make, multiple types of collagen can arise. Although 28 different forms of collagen have been identified, types I-IV are by far the most prevalent; collagen type I represents more than 90% of the human

*Corresponding author E-mail: sara.khan@mithibai.ac.in

body's total collagen [6,7,8]. The three polypeptide chains that make up collagen are referred to as the alpha chain (á). The type of Col is indicated by this denotation. For example, Collagen type 1 is composed of the genes COL1A1 and COL1A2, also referred to as á1 and á2 [9,10]. Glycine-proline-X, also known as glycine-X-hydroxyproline, is the principal amino acid sequence found in the collagen alpha chain [11].

Type 1

Fibrillar type collagen, or type I collagen, has probably been studied the most. The most prevalent kind of collagen, for many tissues to remain structurally intact, type I collagen is vital. It is expressed in the majority of connective tissues and is the fundamental constituent of the interstitial membrane [12]. 90% of the human body is composed of collagen type I (Col-I), the most prevalent type of protein. Common locations for it include the skin, bones, organ capsules, tendons, cornea, and fascia [13,14],excluding cartilaginous tissues [15]. Col-I homotrimers are crucial for the healing of wounds [16]. The predominant isotype of Col type I is heterotrimer, whereas homotrimers of the triple-á helix chain are typically found in embryonic tissue, certain tumors, and fibrotic lesions. This typically occurs because of the homotrimers' strong collagenase resistance, which impedes the cleavage process [17].Col-I is composed of roughly 1000 amino acids and has a length of up to 300 nm and a width of 1 to 5 nm. N telopeptide, C telopeptide, and a central domain makeup Col-I's three domains. This allows for the accommodation of up to 95% of the Col-I molecule structure in the central domains [18]. It may act as a ligand for leukocyte receptor complex LAIR-1, integrins, OSCAR, GPVI, G6b-B, DDR1 and 2, and other receptor-mediated signaling [19].

Mechanical strength

Col-I's tensile strength, temperature resilience, permeability, and catabolism all affect its stability. It is essential to design a bioscaffold that is sturdy enough to not impede biological activities. [20]. The tensile strength of collagen-I derivatives originating from various sources does not significantly differ. Nonetheless, ovine-derived Col-I outperformed derivatives derived from cows, pigs, and rats. The maximum tension measured in Ovine Col-I is 15.08 ± 2.89 kPa, and the proportion of strain is 50.74 ± 4.02%. derivative of pork. The ultimate stress and strain percentage for Col-I are 13.91 ± 3.11 kPa and 47.15 ± 6.20%, respectively, whereas for the bovine it was 12.33 ± 2.37 kPa and 34.87 ± 5.83% [21]. However, according to a study [22], natural collagen type I extracted from rat tails has a contour length of 6.9 ± 2.2 µm, a Young's

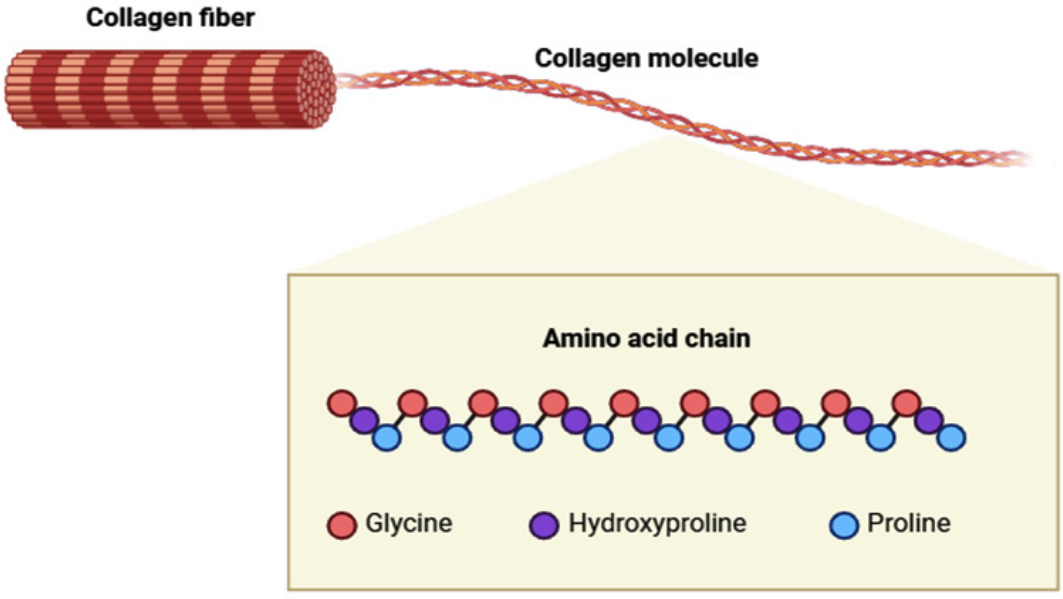

Fig. 1. Collagen structure

modulus ranging from 11 MPa to 95 MPa, and a persistence length of 3.5 ± 0.5 µm.

Surface characteristics

The interaction between the cell and the scaffold surface is essential for tissue regeneration, cell attachment, and proliferation [23]. It is a crucial element that controls the adherence stage of cell response. Instead of adhering to the hydrophobic surface, cells are meant to tether to the hydrophilic one. This is due to the fact that large concentrations of nutrients and water molecules can be retained in a hydrophilic environment. This will be utilized by the cells that are deposited onto the support. As a result, there will be more cell attachment, spreading, and proliferation on the scaffold [24].

Water Vapor Transmission Rate

The Col-I scaffold's moisture permeability is indicated by the Water Vapor Transmission Rate (WVTR). This phase is essential to the healing of wounds because WVTR makes sure the wound has a sufficiently moist surface surrounding it. A healthy drainage of exudate from the injury site is correlated with an ideal range of WVTR. Drawing from the Col type I derived, WVTR varies. Col type I obtained from the scales of fish, for instance, showed 952.6 ± 55.5 g/m2/day and 1090.9 ± 77.1 g/m2/day in porcine samples [25]. Exudates will build up at low WVTR levels, while dehydration will result from excessive WVTR levels as injuries cause water to evaporate. According to research [26] WVTR should be in the optimal range of 2028.3 ± 237.8 g/m2/day in order to support the normal healing phase and preserve a moist environment.

Type 2

The primary component of cartilage is fibrillar collagen, or type II collagen. Cartilage collagen, or type II collagen, makes up 95% of all collagens and roughly 60% of the anhydrous weight. The tissue is resilient to stress and maintains its integrity because of its strength and stability. Members of the matrix metalloproteinase family of collagenases are the main agents responsible for type II collagen cleavage, which yields well-characterized biomarkers like type II collagen's C-terminal telopeptide and C2C. Furthermore, a number of formation makers have been created. Important binding partners for type II collagen include fibronectin and other collagens [27]. In an experiment [28], the mice in the Type 2 collagen group demonstrated a significantly higher level of superiority compared to the mice in the Old model group in terms of motor abilities, including the tremor index (0.42 vs. 1.23), the movement trajectories area (163.25 ± 20.3 vs. 78.52 ± 20.14 cm2), the swing (right front: 0.12 ± 0.02 vs. 0.216 ± 0.02 s), the stride length (right hind: 7.2 ± 0.9 vs. 5.7 ± 1.1 cm), the step cycle (right hind: 0.252 ± 0.05 vs. 0.478 ± 0.11 s), and the cadence (14.12 ± 2.7 vs. 7.35 ± 4.4 steps per s).

Type 3

Unlike most other collagens, type III collagen is fibrillar in nature and has just one collagen á chain. With three á1(III) chains supercoiled around one another in a right-handed triple helix, it is a homotrimer [29]. Within the fibril-forming collagen family, human collagen type III (hCOL3A1) is extensively dispersed throughout tissues with supple connective tissue, such as the circulatory system, internal organs, and epidermis. It is essential for normal human cardiovascular development, collagen fibrillogenesis, and wound healing. The charged residues of hCOL3A1 are thought to be a crucial feature, particularly for collagen binding and recognition [30]. The findings indicate that COL3A1 expression was greater in tumor samples compared to normal samples. A higher stage of cancer and a poorer prognosis are linked to COL3A1 upregulation. Immune cells known to infiltrate tumors (TIICs) include B cells, APCs (Antigen presenting cells), phagocytic cells, cytotoxic T cells, and helper T cells, exhibit strong positive correlations with COL3A1 expression. Different patterns of immune infiltration related to COL3A1 were observed by markers of TIICs [31].

Type 4

The main collagen present in the extracellular basement membranes that divide different types of endothelial and epithelial cells is called collagen IV. It is primarily present in the lamina densa and plays a significant role in the dermal–epidermal junction. A heterotrimeric molecule, collagen IV is made up of one á2-like and two á1-like genes. Collagen IV is linked to six different human genes: COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, and COL4A6 [32]. Three domains can be identified with the á-chains: the C terminal, spheroidal, non-collagenous (NC)-1 region, the middle triple-helical domain, and the amino-terminal 7S region. With 22 breaks within the traditional collagen Gly-X-Y sequence pattern

and a length of approximately 1,400 amino acids (aa), the triple-helical sector is the most extended region. The NC1 region of each á-chain is approximately 230 aa long [33]. A crucial part of the kidney's filtration barrier, the glomerular basement membrane (GBM) is mainly made up of a highly structured matrix of type IV collagen, laminin, nidogens, agrin, and perlecan [34]. It performs BM organization-related tasks and controls the movement of growth factors between different tissue compartments. COL IV is a key modulator of TGF beta's pro-fibrotic actions because it binds to both TGF beta-1 and TGF beta-2 [35].

Use of Collagen supplements

Both internal and external factors are involved in the physiological process of aging epidermis, which is associated alongside a reduction in collagen synthesis [36]. Research has demonstrated that over 75% of the collagen in young, healthy skin is present [37]. The synthesis of collagen fibers is mostly carried out by fibroblasts, which are present in the deeper layers of the skin. Thus, ensuring that the bloodstream receives adequate nutrition is the only method to increase biomatrix renewal [38]. Collagen peptides can currently be obtained from hydrolyzed collagen from cattle, pigs, marine mammals, and poultry [39]. Collagen peptides have experienced tremendous growth in the domestic and global markets. More and more people are becoming aware of collagen peptides' bioactive properties, such as their antioxidative [40,41,42,43],anti-fatigue [44,45,46], hypoglycemic activity [47,48], hypolipidemic activity [49,50], antimicrobial attributes [51,52], and other activities [53,54]. The biomatrix underlying mature skin collapses owing to weakened and unstable collagen framework. Mature skin generates less collagen [55].

Skin

Research has demonstrated that consumption of particular bioactive collagen peptides can reverse the age-dependent decrease in collagen synthesis [56,57,58]. Enzymes hydrolyze natural collagen to create these short chain peptides. Once they are consumed, they are further broken down in the GI tract to create bioactive di- and tri-peptides. These are subsequently let out into the bloodstream and accumulate in the epidermis to conform into the collagen biomatrix [59,60]. Skin care products that are applied topically, like creams, lotions, and sera, frequently fall short of penetrating the skin's deeper layers to significantly and permanently slow down the senescence of the derma. By creating highly biologically available and consequently biologically effective short-chain collagen peptides for nutrition, the goal of reaching

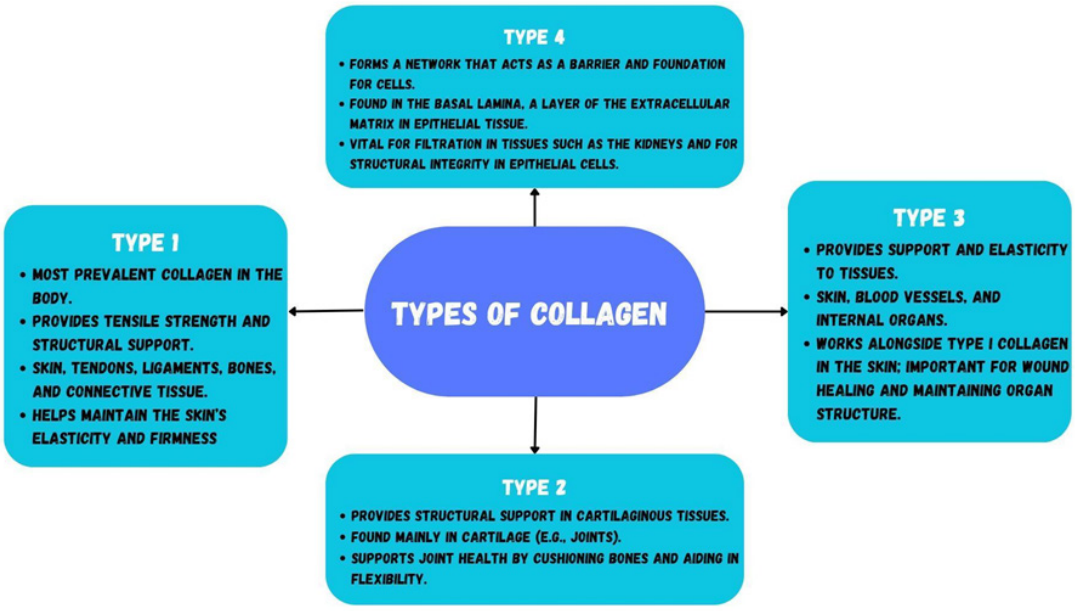

Fig. 2. Types and Function of Collagen

the most important skin layer for the repair of collagen production is the dermis, which has been accomplished [61]. Collagen supplementation was safe and didn't have any known negative effects. According to a controlled, randomised trial [62], consuming 10 g of hydrolysed collagen for at least 56 days improves the skin's degree of hydration and collagen formation when compared to a placebo. A study [63] observed an increase in procollagen type I and elastin when 2.5 g of collagen was consumed daily for 56 days, in comparison to a placebo [64]. As per a research [65], taking 2.5 g of collagen peptides resulted in a statistically significant decrease in the amount of cellulite after 180 days. The high concentration of certain amino acids, such as hydroxyproline, proline, glycine, glutamic acid, alanine, and arginine, which are plentiful building blocks of human collagen, indicates the amino acid composition associated with the peptide [66]. After three months of ingestion, oral collagen peptides along with other dermonutrients considerably enhance dermis moisture, resilience, firmness, and compactness, according to objective dermatological assessments like cutometry and corneometry. A study [67] revealed that the collagen supplement had a high level of safety and tolerability and showed no indicators of toxicity during or after application.

Injuries

Human tendons serve a variety of purposes as a connecting element between muscles and bones [68],and they are necessary for carrying out various movements and locomotor tasks [69]. Apart from conveying muscle contractions to the skeletal structure, tendinous tissue possesses the capacity to accumulate and discharge energy, as well as establish ideal circumstances for maximizing the production of muscle contractions [70]. Supplementing with collagen peptides has been demonstrated to positively impact these anabolic processes. Collagen peptides have been shown in vitro to induce tendon cells to produce ECM molecules like elastin and collagen types I and III [71]. The benefits of supplements made of collagen for tendon architecture and function may be due to collagen peptides' capacity to improve the synthesis of ECM proteins. Collagen peptides exhibit significant resistance to gastroenteric breakdown, enhanced transportation effectiveness, and high bioavailability due to their low molecular weight and high proline and hydroxyproline concentration [72,73,74]. In a case study, after receiving daily dosages of 15 g gelatin and 225 mg ascorbic acid in addition to an 18-month rehabilitation regimen, a basketball player who plays professionally with patellar tendinopathy had a steady drop in patellar at the inferior pole's MRI reactivity. Performance and pain symptoms may have improved as a result [75]. Consuming particular collagen peptides combined with an intense workout regimen greatly reduces lesions in tendons in a current investigation involving patients with Achilles tendinopathy. Furthermore, improvements were noted in the Victorian Institute of Sports Assessment–Achilles (VISA-A) questionnaires for pain symptoms, daily living function, and athletic activity [76]. Furthermore, a study done [77] proved that collagen peptide therapy enhances the perception of ankle function in patients with chronic ankle instability, a condition strongly linked to compromised Achilles tendon biomechanical characteristics.

Forty men volunteers in good health (26.3 ± 4.0 years) underwent a 14-week program of intense resistance training as part of a randomized, placebo-controlled study. A 5g dose daily of specific collagen peptide (SCP) was administered to one group, and a 5g supplement containing a placebo (PLA) was given to the other. Measurements were made of changes in the thickness of the plantar flexors, muscle strength, Cross-sectional area of the Achilles tendon (CSA), and stiffness in the tendon [78]. In comparison to the PLA group (+4.7%), the specific collagen peptide (SCP) supplementation resulted in a notably ($p = 0.002$) larger rise CSA in tendon (+11.0%). Additionally, the statistical analysis showed that the SCP group (+7.3%) had remarkably ($p = 0.014$) a greater gain in muscular mass than the PLA group (+2.7%). Ultimately, the findings indicate that, in young, physically active males, resistance training (RT) combined with specific collagen peptide supplementation is associated with a greater degree of muscle and tendon hypertrophy than RT alone [78].

According to the "mechano-transduction" theory, mechanical strain on tendinous tissue during working out signaling a flow within the cells of the tissue that boosts the synthesis of proteins in matrix and leads to hypertrophy of tendons, suggests that physical activity would likely enhance the advantages of collagen peptides (COL) [79]. Furthermore, because co-ingesting vitamin C aids

in the hydroxylation of proline and lysine collagen synthesis is anticipated to rise [80].

These findings from a study also implies that, when degenerative joint disease is not present, 5 g per day COL may be just as beneficial as 10 g per day COL in reducing discomfort while exercising for athletes [81]. Collagen type I, II and IV , proteoglycan, and elastin synthesis are increased by COL in the cartilage of the joints, which may lessen tissue injury and alleviate pain. This could be one reason for the decrease in joint pain. According to recent study [82], the COL that was utilized had 22% glycine, which is known to improve the organization strength of the collagen matrix, lessen swelling, and affect metabolism of tenocytes in tendons.

A research [83] found that UC-II (undenatured type a! collagen) taken from the sternum of chickens enhanced range of motion for the knee extension (81.0 ± 1.3° vs 73.2 ± 1.9°, COL vs baseline) and longer periods of pain-free exercising (2.8 min vs 1.4 min). In this study, T lymphocytes that are activated and specific to UC-II may have contributed to the beneficial effects of COL. Interleukin-10 and TGF-â, two counter-inflammatory cytokines released by type II collagen, have the ability to block the pro-inflammatory cascade brought on by intense physical activity and cause a shift in the chondrocytes replenishment of the extracellular matrix (ECM).

Chicken sternal cartilage collagen peptides appeared to enhance recovery (8.3 vs. 7.3 points, COL vs. PLA on a perceived recovery scale), lessen signs of a muscular ache that develops slowly (58 vs. 72%, decrease in performance, COL vs. PLA), and attenuate declines in bench-press performance. The COL group also showed decreased levels of plasma biomarkers for inflammation and muscle damage. The intervention group showed a greater ability to endure a regimen of high-intensity resistance training, suggesting that COL may quicken the "repeated bout effect" protective adaptation and promote improved musculoskeletal recovery through potential ECM remodeling [84]. Research evaluated how COL affected the synthesis of muscle proteins and collagen. A recent study [85] discovered that when taking 15 g per day of ascorbic acid enriched COL instead of 5 g/day of PLA, collagen production rose and stayed elevated for 3 days. For collagen synthesis, vitamin C is necessary because it stimulates and facilitates the synthesis of hydroxyproline and collagen cross-linking as vitamin c acts as a coenzyme. The rise in indicators of bone collagen production (PINP) (153% increase with 15 g COL, vs. 59.2% increase with 5 g COL and 53.9% increase with PLA) shows that the collagen production was elevated by the 15 g per day COL during the post-exercise recovery period. This suggests that consuming 15 g of COL per day along with sporadic physical activity, starting 60 minutes before physical activity, might improve tissue healing and reduce the risk of injury.

A study [86] found that collagen increased the amount of proteins (such as myosin proteins, actin-binding proteins, and tropomyosins) connected to resistance exercise adjustments using skeletal muscle proteomics. This is probably because collagen peptide supplements contain a high concentration of hydroxyproline peptide [87].

Wound healing

Prolonged wounds can result in considerable morbidity and a reduced standard of living. Because of abnormal protease levels, an extended and heightened inflammatory reaction, and inadequate extracellular matrix, chronic wounds may not respond to standard therapy [88]. Novel wound treatments are being developed. One of the biomaterials that is highly helpful for creating cutting-edge treatments is collagen. Collagen sponges' wet strength made it possible to suture soft tissue and served as a template for the formation of new tissue. Drugs for burn treatment and skin replacement have been delivered via collagen-based implants [89]. Collagen dressings were simple to use and remove, typically made with collagen from pigs, birds, or cows [90]. Furthermore, the marine source could be used to make collagen dressings. One of the most widely cultivated fish in China is nile tilapia, and the skins of these fish can produce collagen hydrogels that can be applied to wounds to treat deep second-degree burns [91]. Oral collagen supplementation may also be a successful wound healing treatment. A study was done to find out how wound healing was impacted by ingesting collagen peptides derived from jellyfish. [92]. Collagen peptides from jellyfish (*Rhopilema esculentum*) have shown an excellent ability to accelerate wound healing, suggesting that they may prove useful in future wound clinics. In

wound rat models, researchers investigated the possibility of oral administration of skin-derived collagen peptides from chum salmon to enhance wound healing [93]. The result showed how lingual collagen peptide treatment improved animal wound recovery. Additionally, it has been shown that some bioactive collagen peptides promote wound healing when taken orally. According to a study, patients who received bioactive collagen peptide treatment fared better than those who received a placebo [94]. A study found out that Prolyl-hydroxyproline, or Pro-Hyp, is a peptide derived from collagen that stimulates the growth of certain fibroblasts that are involved in the healing of wounds [95].

Bone defects

The aging population is driving up the costs and complexity of bone-related medical treatments. Calcium phosphate is the mineral phase and collagen is the organic phase that makes up bone. The development of scaffolds with good biological and biomechanical properties is a challenge in bone tissue engineering [96]. Cellular substances should permit appropriate bone repair by colonisation of host cells, and scaffold architecture is crucial for bone regrowth. Average pore size is an additional essential element for successful colonisation of cells. The pore size of collagen-glycosaminoglycan scaffolds significantly improved [97]. Regenerating large segmental bone defects is one of the main obstacles in clinical orthopaedics. Collagen scaffolds are being utilized more often in tissue engineering techniques to replace missing bone [98]. Collagen composite scaffolds with exceptional mechanical properties were demonstrated by the synthesis of composite constructions made of calcium and collagen catecholamines, as stated [99].

These scaffolds with multiple uses could be used to regenerate and restore bone defects. The collagen matrix's osteogenic, structurally stable, permeability, and osteoinduction qualities can all be significantly enhanced by combining various biological materials [100]. Alveolar clefts are defects in the development of the bones, and they are typically repaired using autologous cancellous bone taken from the iliac crest [101]. The application of synthetic bone replacements has not proven to be more advantageous than autologous bone transplant hence the need for novel bone replacements persists. [102]. Since type I collagen makes up a significant portion of bone, type I collagen based bone replacements are a suitable alternative.. Conventional collagen scaffolds made from xenogeneic tissues, however, may raise the possibility of unidentified infections [103,104,105]. Utilizing human type I collagen, a recombinant collagen peptide (RCP) was created [106]. A researcher discovered that in contrast to RCP particles with little or strong cross-linking, the environment for the medium cross-linked RCP particles was more favourable for the development of bone tissue [107].

Dental treatments

Adults are highly susceptible to the highly common disease periodontitis, which has an impact on the tissues that surround the teeth and is typically brought on by a bacterial infection. It can result in tooth loss if untreated. Many biomaterials have been studied for their potential application in periodontal regeneration over the years. Periodontal disease treatment options include scaling and root planing, physiologically materials that actively regenerate, graft material for bone replacement, open flap debridement (OFD), and using barrier membranes to guide tissue regeneration [108,109,110,111,112,113]. Periodontal regeneration was performed in accordance with guided tissue regeneration principles through the use of two horse collagen membranes in combination with a horse bone transplant. Collagen membrane application has been shown in this case to enhance bone regeneration at the defect site. Additionally, a basic poly-lactic-co-glycolic acid and polycaprolactone matrix was electrospun to create a scaffold, which was then coated with collagen I, impregnated with silver nanoparticles, and coated with polydopamine [114].

Gingival recession (GR), which is often observed in adults,is the root surfaces being visible due to the gingival tissue edges migrating apically [115]. The combination of a coronally advanced flap (CAF) and connective tissue graft (CTG) is the standard treatment for GR. A collagen bioscaffold was employed to treat GR [116]. For GR, cellular adhesion, movement, and viability inside the scaffold are influenced by the cell adhesion within the scaffold. It was discovered that collagen was a better bioscaffold for treating GR. Porcine collagen matrix plus CAF treatment did not differ statistically significantly from CTG plus CAF treatment at the 12-month mark in a prospective,

randomized, controlled clinical trial involving 18 adult patients [117].

The most common oral surgery, third molar extractions can occasionally result in serious or minor complications. When using type I collagen sponge that is absorbent for excision of the third molar, a retrospective study assessed the rates of postoperative complications [118]. Collagen type I sponges were used to fill the extraction sockets after 2697 patients had their 3869 third molars extracted. According to the study, using collagen type I sponge had a comparatively low incidence of complications [119]. The outcome demonstrated that it could lessen discomfort, lessen the occurrence of mouth-opening restriction, and raise the extraction socket site's mineralization ratio. Additionally, porcine collagen matrix is used in a prospective observational (non-controlled) clinical research conducted on 15 patients to rebuild keratinised tissue surrounding dental implants. [120].

Gastroesophageal reflux disease (GERD)

The medical illness commonly referred to as gastro-oesophageal reflux disease (GERD) is brought on by acidic stomach contents that reflux up into the esophagus from the stomach. GERD has been linked to major depression and is a risk factor for esophageal cancer [121,122]. The gene for type III alpha 1 collagen has been linked to GERD. Moreover, the hiatal hernia contributes to the development of GERD and acid reflux. 94% of people with GERD also have a hiatal hernia. A study [123] demonstrated that people with GERD with a hiatal hernia had less total, type-I, and type-III collagen in their phrenoesophageal ligaments (POL) than cadavers without a hiatal hernia.. Because of its demonstrated tissue biocompatibility and persistence, a composite material known as Collagen/PMMA implant (G125), which consists of PMMA (polymethyl methacrylate) microspheres which are spherical and smooth, floating in a collagen "carrier," has shown promise as an endoscopic "bulking agent" for the treatment of GERD [124]. Permanent submucosal soft tissue augmentation of the lower esophageal sphincter can be achieved with G125, and during the vital month-long stage of tissue remodeling following injection, the microspheres can be prevented from both migrating and aggregating by the collagen carrier material derived from cows. Consequently, collagen scaffold was crucial to the implant injection used to treat GERD [125].

Osteoporosis and osteoarthritis

Decreased skeletal mass and a decline in bone health in terms of both anatomy and structure are the hallmarks of osteoporosis (OP), a skeleton disease with multiple underlying causes that increases bone fragility and fracture risk. Older women are the most affected by OP because their decreased estrogen production after menopause causes an acceleration of bone loss [126]. Osteoarthritis (OA) is the most common joint disease. It develops gradually over decades, starting with painful episodes and ending with loss of joint function. Studies that are not entirely conclusive suggest that changes in the bone may cause or contribute to cartilage degradation. The treatments for osteoarthritis (OA), both pharmaceutical and non-pharmacological treatments only function to reduce the symptoms, including pain, swelling, and immobility., despite numerous attempts to find a cure [127,128]. The body's collagen levels can be impacted by age and poor diet. The mature phase of life is when these changes become apparent, as food intake no longer adequately meets recommended requirements for energy and macro- and micronutrients. The early years of life are not marked by these changes [129]. The most prevalent type of collagen in connective tissue is called tropocollagen, which is also a source of gelatin and collagen hydrolysate that has been partly hydrolysed. Collagen hydrolysate is dissolved in water or brine, whereas gelatin is not, making it easier for the body to absorb and digest while also allowing it to create collagen from free amino acids [130]. The presence of proline and glycine in collagen hydrolysate's composition is one of its most significant characteristics. The stability and regeneration of cartilage depend on these amino acids [131]. A study [132] claims that type I collagen makes up 80% of human connective tissue and 25% of the body's total protein. In addition to improving bone mineral density and content, collagen type I synthesis also plays a significant function in the differentiation of osteoblasts by raising the quantity of collagen type I in the bone matrix. Research [133] states that hydrolyzing the collagen is necessary for the administration of collagen to have a positive effect. They found

that proteins are crucial for maintaining healthy bones and preventing osteoporosis throughout their mice in vivo research. Increased proliferation and osteoblastic cell differentiation and decreased numbers of osteoclastic cells are the results of collagen's modulation of bone formation and mineralization of the bone matrix. Every collagen that was tested had the capacity to raise osteoblast activity. A researcher [134] measured the amounts of glycine hydroxyl (Hyp-Gly) and hydroxyproline (Pro-Hyp) in the blood after oral CH consumption in five healthy individuals. Blood samples were taken before, 30 minutes, 1, 2, and 4 hours after the volunteers consumed 8g of CH dissolved in 100ml of water. An hour passed before the concentrations of Pro-Hyp and Hyp-Gly in plasma peaked at 6.1% and 22.1%, respectively. In a study [135] it was found out that not only do amino acids get absorbed through oral ingestion of CH, but di- and tripeptides are also retained in human peripheral blood for a considerable amount of time. These peptides are believed to have a chondroprotective effect on articular cartilage in addition to stimulating the synthesis of hyaluronic acid in cultured dermal fibroblasts and synovial cells. They also promote cell growth and proliferation.

Anti-Atherosclerotic Activity and Anticoagulant activity

A major contributing factor to ischemic heart disease and stroke is atherosclerosis, a chronic inflammatory disease driven by lipids that develops as plaques throughout the major and middle arteries. It mostly affects the arteries' bends and branches, where it can cause the vessels to rupture or become blocked. It therefore presents one of the greatest dangers that cardiovascular disease poses to human health [136]. By 2021, about 2 billion individuals will have carotid atherosclerosis, based on a recent study that was released in The Lancet's sub-publication. The study assessed the risk factors and prevalence of carotid atherosclerosis in 21 populations in the country and the region around the globe. Atherosclerosis poses a major risk to human longevity, health, and quality of life [137]. Collagen peptides isolated from Atlantic salmon skin were discovered to have strong anti-atherosclerotic properties, as they prevented the development of fat buildup in the thoracic aorta and intimal thickening in the aortic arch [138]. Skin-derived oligopeptides separated from mackerel [139], and silver carp [140], have all been shown to have anticoagulant activity. The three oligopeptides from the skin of silver carp, which are absorbed by Caco-2 and are not rendered inactive by digestion in the stomach, inhibited platelet aggregation induced by thrombin and adenosine diphosphate in a dose-dependent manner, but did not affect platelet release. Despite being less potent than Argatroban, it also considerably extended TT, PT, and APTT. Furthermore, a significantly higher ($p < 0.05$) platelet aggregation inhibitory activity (~30%) was demonstrated by the 60 mg/mL tripeptide, which was comparable to synthetic antithrombotic drugs like aspirin and indomethacin [141]. In an experiment [142] the molecular weights of peptides with anticoagulant activity are typically less than 2.5 KDa and less than 3.5 KDa. Therefore, using ultrafiltration, microfiltration, or nanofiltration to produce low molecular weight peptides with strong anticoagulant activity appears beneficial.

Anti diabetic activity

Lethargy, polyuria, polyphagia, and excessive drinking are common symptoms of diabetes mellitus (DM), which is primarily characterized by elevated blood glucose levels. Chronic problems involving the tissues such as the cardiac, neural, hepatic, kidney, spleen, retina, neurological system, skeletal muscle, and blood vessels will result from long-term, persistently high blood sugar [143]. The clinical treatment of diabetes involves a broad range of medications, such as alpha-glucosidase inhibitors, biguanides, insulin promoters, and insulin sensitizers. There are many different kinds of clinical diabetes medications, but there may be problems with their efficacy, mechanism of action, and unfavorable side effects. Consequently, there is an increasing need to find natural hypoglycemic agents that are safe and effective to replace artificial ones [144]. Collagen peptides have been found to be useful in reducing the symptoms of diabetes, despite the fact that soy and milk protein are the most well known sources of antidiabetic peptides. [145]. Similarly, a study found that glucagon-like peptide 1 (GLP-1) could be released in vitro by protein hydrolysates extracted from the skin gelatin and excipients of Atlantic salmon (*Salmo salar*). Since glucosidase and alpha-amylase are few of the objectives of diabetic treatment, hypoglycemic activity manifests in vitro as the inhibition of either

enzyme. The molecular weights of the majority of antidiabetic peptides are less than 1 KDa [146]. At a concentration of 1 mg per mL, collagen peptides generated by collagenase hydrolysis demonstrated CP-5 had antidiabetic activity of 80.45%, in contrast to 75.81% and 71.17% for CP-25 and CP-50, in that order, as determined by the inhibition of á-amylase [147]. An experiment [148] demonstrated that during a three-month study period, taking 5 g of collagen peptide (CPT) significantly decreased the subjects' glycated hemoglobin and fasting blood glucose. This was determined in a double-blind, randomised trial that evaluated the effectiveness of CPT as a nutritional supplement in patients with type 2 diabetes.

Sources

Marine

The majority of collagen that was previously accessible was taken out of leftovers from the processing of pigs and cows, but in the last few decades, there has been less use of collagen from these sources. Dietary restrictions may occasionally be imposed because of individual needs or preferences regarding the use of products derived from pigs and cows. Due to religious prohibitions, it is not allowed for 38.4% of the world's population are either Muslims, Hindus, or Jews [149]. Because there are no religious restrictions on their use and no reports of potentially transmissible diseases, marine organisms have recently drawn attention as promising sources of collagen. Specifically, the biomass obtained from fisheries and fish-processing industries (fish and sea urchin wastes, undersized fish, and creatures that are caught by accident, such as sponges, jellyfish, sharks, and starfish) may prove to be a significant, albeit underutilized, collagen source [150,151,152,153,154,155]. The annual production of fish waste produced by the fish processing industries is estimated to be 25%. More than 70% of the waste is made up of fish bones, skin, scales, and fins. Because they nearly have the same protein content as fish flesh, some of these wastes are currently used as feed [156]. Both its natural fibrillar form and its denatured form are utilized with marine collagen. Numerous post-translational changes that collagen undergoes during biosynthesis are essential to the protein's structure and biological activities [157]. Denaturation provides the ability to create multiple forms of collagen, such as sheets, tablets, pellets, and sponges. When collagen's triple helix structure is broken down into single-strand molecules by acid, alkaline, or enzymatic hydrolysis, a water-soluble gelatin is created. By using heat and mechanical stresses in extrusion-based technologies, thermal plasticization techniques make it simple to process gelatin [158]. A particular emphasis is on the bioactive properties of marine collagen, which are being studied in preclinical and clinical trials and could eventually result in an increase in demand for this biomaterial [159].

Bovine

The primary byproduct of the cow processing industry is bone, which is extensively utilized as a raw material to produce gelatin of superior quality [160]. Bovine bone is still one of the most common sources of gelatin and makes up 23.1% of the gelatin produced, despite some worries about mad cow disease in Europe and the US [161]. As a result, bovine bone is a plentiful and superior raw material used in the production of CPs. The primary focus of CPs derived from bovine bone is their advantageous impact on bone metabolism, which includes preventing bone loss and mitigating the symptoms of osteoarthritis [162,163]. For the first time, research has shown that CP compounds isolated from bovine bone with molecular weights ranging from 0.6 to 2.5 kDa can stimulate osteoblast differentiation and proliferation in vitro. In the current investigation, we first discovered that bovine CP compounds significantly and dose-dependently increased osteoblast growth [164]. Based on a recent study [165] it was found that human osteoblastic cell line MG63 cells were stimulated to proliferate when collagen hydrolysate (CH) with molecular weights of less than 3 kDa was extracted from pig skin gelatin.

Future Prospects of Collagen: Research and Trends

1. Collagen in Skin Care and Anti-Aging: Formulations using peptides, hydrolysed collagen, or collagen-derived amino acids are becoming more popular due to their capacity to reach deeper layers and promote collagen production in the dermis, even though large collagen molecules are often too massive to be absorbed by the skin[166]. It has been demonstrated that oral collagen supplements, usually in the form of hydrolysed collagen peptides, increase skin hydration, suppleness, and wrinkle

appearance. According to clinical research, collagen peptides may promote the body's natural production of collagen, particularly when taken regularly over an extended period of time [167,168].

2. Collagen in the Food Industry: Every year, industrial processing produces a significant volume of food-grade animal by-products, which are often used for low-value applications like animal feed. Collagen and gelatin are two examples of the important proteins found in these byproducts. The establishment of a high benefit-to-cost ratio might result from the revalorization of collagen [169].

3. Sustainability and Ethical Sourcing of Collagen: Although collagen is not found naturally in plants, the body may produce more of it with the help of several plant-derived substances. Collagen supplements are increasingly being replaced with plant-based collagen boosters, such as amino acids like proline, glycine, and vitamin C. Biotechnology developments might make it possible to produce collagen via tissue engineering or microbial fermentation, providing a cruelty-free and more sustainable substitute for collagen obtained from animals. Although this technology is still in its infancy, it has a lot of promise for the future [170].

Potential benefits

1. Skin: When compared to placebo treatments, a study of 19 research including 1,125 participants (95% women) aged 20 to 70 years revealed that hydrolysed collagen reduces wrinkles, skin moisture, and suppleness [171]. Collagen dosages that have been found to be beneficial for enhancing skin health vary, although most studies have utilized 2.5–15 grams daily for at least eight weeks [172,173].

2. Bone: In one study, 102 postmenopausal women with decreased bone mineral density (BMD) were examined to see how taking collagen supplements affected them. In comparison to those who received a placebo, those who took 5 grams of collagen peptides daily for a year saw notable improvements in bone mineral density (BMD) in their femur (a bone in the lower leg) and spine [174]. During the follow-up period, the study [175] discovered that participants' BMD rose by 1.23–4.21% in the femur and 5.79–8.16% in the spine.

3. Wound healing: The therapeutic effects of conventional dry dressing therapies, including absorbent cotton and absorbent gauze, may not be very good. Instead, the lesion healed more quickly in a wet healing environment because it encouraged the formation of granulation and the division of skin cells. It has been shown that collagen hydrogel is a promising wet wound dressing material that might greatly speed up the formation of new skin appendages [176] .

Limitations

1. Transmit diseases: Sources of collagen derived from animals carry the danger of disease transmission. Collagen derived from pork and cows has the potential to spread diseases like bovine BSE. It has been shown how ruminant collagen and gelatine made from raw materials for human use might increase the risk of BSE [177].

2. Allergen: The findings revealed that immunoglobulin E (IgE) against mackerel collagen was present in 50% of Japanese fish allergy patients, whereas IgE against mackerel parvalbumin was present in 44%. High cross-reactivity of mackerel collagen to 22 fish species was found using the IgE inhibition experiment [178]. Even when fish flesh was subjected to a high heating load, the patients' sera's IgE reactivity to fish collagen in extracts remained maintained. Regarding fish collagen, cartilaginous fish had reduced IgE reactivities compared to bony fish. It is challenging to reduce IgE reactivity to fish flesh using heat; thus, alternative methods will be needed to create hypoallergenic fish meat [179].

CONCLUSION

In conclusion, the extensive exploration of the role of collagen in health and disease underscores its paramount significance in maintaining tissue integrity and functionality. Collagen, as a primary structural protein in the extracellular matrix, not only provides mechanical support but also plays a pivotal role in cell signaling and homeostasis. The intricate interplay between collagen and various cellular processes highlights its multifaceted impact on overall health. Additionally, dysregulation of collagen synthesis or degradation is implicated in a spectrum of diseases, ranging from connective tissue disorders to cancer. A comprehensive understanding of the diverse functions of collagen is essential for unraveling novel therapeutic strategies and interventions aimed at preventing or ameliorating collagen-related pathologies. As research continues to unveil the intricate complexities of collagen biology, it becomes increasingly evident that

targeting collagen pathways holds great promise for advancing our ability to manage and treat a wide array of health conditions.

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This research does not involve any clinical trials**.**

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