



Endogenous Synthesis of Collagen and its Relation to Aging: A Systematic Review

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Abstract: The aim of the study was to carry out a systematic review of the literature on the interrelation between the production of endogenous collagen and the mechanisms of human aging. The methods involved Systematic search on the electronic database PubMed and Scopus in order to select published articles on the endogenous synthesis of collagen and the molecular cascades responsible for aging, following the items of the Guidelines for Systematic Reviews and Meta-analysis (PRISMA). As for the results, 885 articles were identified in the searched databases (858 in PUBMED and 27 in SCOPUS). After exclusion by abstract and title, 62 articles were selected for analysis of the full text. At the end, 13 articles were chosen as relevant to compose the qualitative synthesis. The articles pointed out that collagen synthesis occurs in processes of regeneration and formation of embryonic tissue. Regarding the relationship between such production and aging, advancing age reduces the mechanical strength of fibroblasts due to the accumulation of fragments of collagen fibers in the intercellular spaces, as well as being associated with alterations in the proportions of type 1 and type 3 collagen levels. Collagen synthesis may still be susceptible to interference of environmental and genetic factors, such as nutrition, hormone levels, UV radiation and mutations. Finally, hydrolyzed collagen (HC) supplementation was associated mainly with maintaining skin health. Conclusions are that the synthesis and molecular levels of collagen are modified due to aging. In this context, environmental and genetic factors are also active in modifying these levels and production. To mitigate some effects of the skin aging process, hydrolyzed collagen supplementation is being indicated as effective.

Keywords: human aging, collagen; endogenous synthesis.

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Síntese Endógena do Colágeno e sua Relação com o Envelhecimento: Uma Revisão Sistemática

Resumo: O objetivo do estudo foi realizar uma revisão sistemática da literatura sobre a inter-relação entre a produção de colágeno endógeno e os mecanismos do envelhecimento humano. Os métodos envolveram busca sistemática na base de dados eletrônica PubMed e Scopus para selecionar artigos publicados sobre a síntese endógena de colágeno e as cascatas moleculares responsáveis pelo envelhecimento, seguindo os itens do Guidelines for Systematic Reviews and Meta-analysis (PRISMA). Quanto aos resultados, foram identificados 885 artigos nas bases de dados pesquisadas (858 na PUBMED e 27 na SCOPUS). Após exclusão por resumo e título, 62 artigos foram selecionados para análise do texto completo. Ao final, 13 artigos foram escolhidos como relevantes para compor a síntese qualitativa. Os artigos apontaram que a síntese de colágeno ocorre em processos de regeneração e formação do tecido embrionário. Quanto à relação entre tal produção e o envelhecimento, o avanço da idade reduz a resistência mecânica dos fibroblastos devido ao acúmulo de fragmentos de fibras colágenas nos espaços intercelulares, além de estar associado a alterações nas proporções dos níveis de colágeno tipo 1 e tipo 3. A síntese de colágeno ainda pode ser suscetível à interferência de fatores ambientais e genéticos, como nutrição, níveis hormonais, radiação UV e mutações. Por fim, a suplementação de colágeno hidrolisado (HC) foi associada principalmente à manutenção da saúde da pele. As conclusões são que a síntese e os níveis moleculares de colágeno são modificados devido ao envelhecimento. Nesse contexto, fatores ambientais e genéticos também atuam na modificação desses níveis e produção. Para mitigar alguns efeitos do processo de envelhecimento da pele, a suplementação de colágeno hidrolisado está sendo indicada como eficaz.

Palavras-chave: envelhecimento humano, colágeno; síntese endógena.

Introdução

Collagen is one of the most important proteins present in the human body. It is the main constituent of the extracellular matrix of connective tissue and, thus, found in the most diverse tissues, such as tendons and ligaments, in addition to being a protein of fundamental importance for the healing process (Sorushanova et al., 2018). This substance contains peptide chains of the amino acids glycine, proline, lysine, hydroxylysin, hydroxyproline and alanine. These chains are organized parallel to an axis, forming collagen fibers, which is the result of the entire process of endogenous synthesis (Albaugh et al., 2018).

Diverse healing mechanisms, in order to maintain the shape and integrity of the tissue, has, as its principal agent, the collagen protein. Therefore, these physiological processes are dependent on the endogenous synthesis of collagen for their execution, with fibroblasts being the major secretory cells of this substance to the extracellular environment. However, this endogenous synthesis can be compromised by several factors, both external and internal, being related to hormonal, nutritional and solar radiation issues, thus compromising the normal functionalities of the fiber under analysis (Holmes et al., 2018).

Due to an increase in life expectancy worldwide, caused by the advancement of medicine in terms of decreasing morbidity and greater longitudinal care of patients, demonstrated by the United Nations estimates that present data in 2011 compared to data from the projected elderly population for 2040/2050, with the share of the population having 80 years or more in 2011 representative of 1.6% of the world population and projections accusing it to increase to 4.3% in 2040. Moreover, again according to the United Nations, in 2011 the portion of the population that corresponds to 60 years old or more represented 11% of the total population and in the year 2050 this segment of the population will represent 22% (United Nations, 2015). Thus, collagen becomes a major object of studies for research in several areas, but mainly in those whose focus of their investigations is the use of collagen supplementation, in the form of hydrolyzed collagen (HC). This is studied with the objective of delaying aging, especially of the skin, aiming to reduce the marks of this process in the human body.

Researches with collagen are recurrent in a search for improvements in bone degeneration conditions, such as osteoarthritis, which are caused by a deterioration in the connective tissue that forms the articular cartilage and by bone alterations (Porphyry & Fanaro, 2016), and in muscle injuries, in which experiments performed on animals, through HC supplementation, bring promising results, demonstrating that there is an increase in regenerative activity in these conditions in addition to a reduction in the inflammatory process that affects these tissues (Clifford et al., 2019).

Collagen-related researches are not limited to its use as a supplement, but they also aim to understand genetic factors, such as the influence of the growth hormone (GH) (Chen et al., 2018), and environmental factors, such as solar radiation, that influence from the synthesis to the degradation of this protein (Albaugh et al., 2017), aiming to understand the implications of changes in these factors, which may result in possible damage to the involvement pathways of this protein in the human body.

The design of this review followed the acronym PICO to delimit the of the review, being defined as “What does the scientific literature present regarding the physiological synthesis of collagen in the human body and what is the relationship of this process with aging?”. In this context, this study aims to conduct a systematic review of the literature on endogenous collagen synthesis and its implications for aging, seeking to highlight the environmental and genetic factors that may have relevant implications for collagen protein synthesis.

Methodology

Search strategy and inclusion criteria

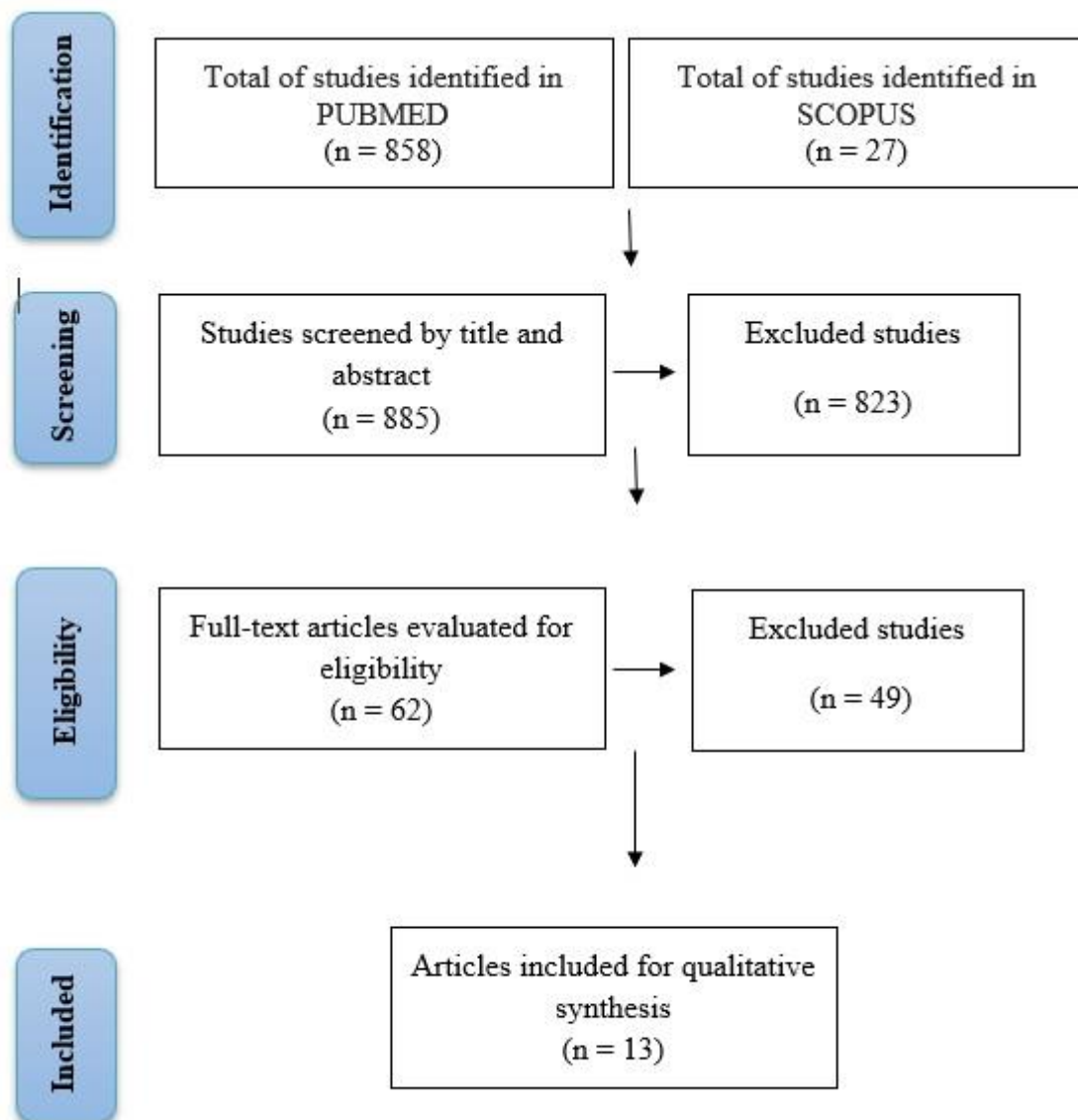
A systematic search was conducted in the electronic databases of PUBMED and SCOPUS to select published studies on the endogenous collagen synthesis and its relationship with aging, following the items of Guidelines for Systematic Reviews and Meta-analyzes (PRISMA). There were two independent reviewers and a third reviewer consulted in cases of articles of conflicting interest. The keywords “Collagen” AND “physiology” AND “synthesis” AND “aging” were applied to identify all articles published on the theme proposed by this review until April 2020. When the words were crossed, the Boolean expression “AND” was adopted (insertion of two or more words).

The inclusion criteria for studies were: (1) original studies with primary data (2) indexed articles; (3) studies with specified methodological rigor (4) articles published in English. Studies with methodological bias and conflicting results were excluded from this work. Data related to endogenous collagen synthesis, the physiology of aging, evidence of collagen supplementation and its implications for endogenous synthesis, relating to genetic and environmental aspects of this process, were extracted.

Results

A total of 885 articles were retrieved using the search strategy. Out of these, 858 indexed in PUBMED and 27 in SCOPUS. After sorting by title and abstract, 62 articles were selected for evaluation of full text. Out of these studies, 49 were excluded for lack of information regarding the objective studied in this review. Thus, 13 articles were included for active qualitative synthesis (Figure 1). In addition, 10 of the selected studies in the final sample are indexed in the PUBMED database, while 3 studies are indexed in SCOPUS. The main characteristics of the included studies are presented in Table 1.

Figure 1 - Flowchart of article selection.



Fonte: Adapted from Moher *et al.* (2009).

Table 1. Summary of articles selected by the search strategy.

Author and year	Country	Objective	Study design	Results	Key Evidence
Li et al., 2015	USA	Investigate the relationship between the spreading force in fibroblasts and PGE2 synthesis	Acquisition of tissue from healthy human buttocks/analysis of microarrays of cDNA/Laser capture microdissection (LCM) in 30 tissue sections.	The expression of IPTGES1 mRNA increases progressively during aging in human skin in vivo.	The study suggests that the reduced mechanical strength/scattering of fibroblasts on aged skin increases the production of PGE2, contributing to the reduction of collagen production.
Oba et al., 2015	Japan	To evaluate the water content in the stratum corneum and the skin elasticity in mice.	Rats were kept in cages with an average room temperature of 24°C. The rats received an AIN-93G diet and water. Subsequently, there was an analysis of the dorsal skin of the dead rats. All rats were killed under anesthesia.	Supplementation of hydrolyzed collagen brought significant benefits in the control of water of the stratum corneum	Long-term administration of hydrolyzed collagen improves skin quality by regulating genes related to the production and maintenance of this tissue
Proksch et al., 2014	Germany	Study the supplementation of hydrolyzed collagen in skin improvement, in relation to skin aging.	69 women between 35 and 55 years old were randomly selected to receive either 2.5g or 5g of hydrolyzed collagen or placebo once daily for 8 weeks.	At the end of the study, the two groups that were supplemented with hydrolyzed collagen had significant improvements in skin elasticity when compared to the control group.	Supplementation of hydrolyzed collagen in an attempt to improve the skin against aging is of great value, bringing benefits mainly in the elasticity of this tissue.
Shigemura et al., 2014	Japan	Examine the beneficial dose of hydroxyproline from hydrolyzed collagen supplementation.	Four volunteers taking doses of hydrolyzed collagen. The doses were 30.8, 153.8 and 384.6 mg/Kg	The plasma hydroxyproline concentration is dependent on the administered dose, reaching maximum levels of 6.43, 20.17 and 32.84 nmol/ml after ingestion of 30.8, 153.8 and 384.6 mg of hydrolyzed collagen.	Ingestion of less than 31mg of hydrolyzed collagen has no significant health effects
Vestergaard et al., 2012	Denmark	Investigate whether the local application of growth hormone stimulates the synthesis of tendon collagen in elders.	Application of circulating growth hormones in elders compared to a group of elderly people who were given a placebo.	In the first six hours after the last injections, there was a tendency for a higher tendon collagen.	Local rhGH injections increase collagen synthesis in the tendon directly or indirectly, increasing local bioactive IGF-I.

Hansen et al., 2012	Denmark	Study local IGF-1 injections to prove that this substance is able to stimulate the synthesis of tendon collagen	Participation of 12 non-smokers/application of two injections of human recombinant IGF-1 each or saline solution (for the control group), with an interval of 24h	Fractional tendon collagen rate was significantly higher in tissues that received IGF-1 compared to those that received saline	Direct application of IGF-1 is able to directly increase the production of tendon collagen.
Wilson et al., 2012	USA	Investigate the effects of structural changes in collagen due to the aging process, in addition to the properties and capabilities of cell contraction in collagen hydrogel constructions reconstituted by a nondestructive method.	A nondestructive indentation technique and optical coherence tomography (OCT) is used to determine the elastic modulus and dimensional changes.	Younger collagen productions have a higher elastic component and greater contraction compared to older collagen.	Aging has a direct effect on the mechanical properties of collagen.
Wang et al., 2011	China	Examine the quantity and distribution of type I and type III collagen in the skin, both in lesions and in hypertrophies.	Examine tissue samples of human skin, in hypertrophic healing or burned. The skin was obtained from aborted fetuses and burned patients.	The results show that there is a variation in the concentration of collagen types I and III during aging, with collagen type III decreasing with aging.	The skin of elderly people is more fragile, thin and flabby, in addition to being more susceptible to wounds and imperfect healing processes, since the levels of collagen types I and III, which have fundamental roles in the formation process of healing tissue, decrease as age advances
Zague et al., 2011	Brazil	Investigation of the effect of hydrolyzed collagen supplementation on skin extracellular matrix proteins	Male four-weeks-old rats were fed a specific modified AIN-93 diet containing casein or collagen for four weeks.	The amount of type I and type IV collagen increased after supplementation with hydrolyzed collagen, but this supplement did not influence MMP-9 activity.	Ingestion of hydrolyzed collagen may be associated with reduced age-related changes in the extracellular matrix.
Guilleminet et al., 2011	France	Evaluates the effects of hydrolyzed collagen supplementation on bone health of ovariectomized mice.	Supplementation of hydrolyzed collagen for ovariectomized mice. The animals were divided into two groups, the first one had supplementation for 6 months and the second one for 3 months.	Even after twenty-six weeks of ovariectomization, ingestion of hydrolyzed collagen was able to improve bone mineral density.	The study concluded that hydrolyzed collagen supplementation is able to reduce bone density loss.

Knuutinen et al., 2002	Finland	Compare collagen synthesis and degradation in smokers and non-smokers.	Study population comprised of 47 smokers and 51 non-smokers. Use of a suction bubble in the arm to collect liquids for the analysis of biochemical compounds.	Type I and type III collagen analyzes from the suction bubble were considerably lower in smokers than in people who never smoked.	Smoking is able to decrease type I and type III collagen synthesis, also changing the balance of the extracellular matrix in the skin.
Yin et al., 2000	Japan	Study the relationship between tobacco extract smoke and skin fibroblasts.	Fibroblast samples from three non-smoking individuals of different ages and genders (male-41 years old/female-73 years old/female-75 years old) were exposed to tobacco extract smoke.	Tobacco extract smoke induces the expression of MMP-1 and MMP-3 in human skin fibroblasts.	Tobacco extract smoke amplifies the cutaneous loss of collagen, due to the change in the proportion between MMPs/TIMPs, favoring the formation of a favorable environment for degradation and continuous loss of collagen in the skin.
Verzijl et al., 2000	USA	Establish the effect of the turnover rate on the accumulation of CML, CEL and pentosidine in cartilage and skin.	Comparison of the degree of racemization of aspartic acid in cartilage and skin collected.	The increase rate of AGEs was higher in cartilage collagen than in skin collagen, indicating a lower turnover and a longer permanence of the studied proteins in the cartilage.	In both cartilage and skin, AGE levels (CEL, CML and pentosidine) are linearly related to aspartic acid racemization levels, a direct measure of protein permanence, which implies that protein turnover is an important factor for AGEs accumulation.

Source: Authors, 2020

Endogenous collagen synthesis

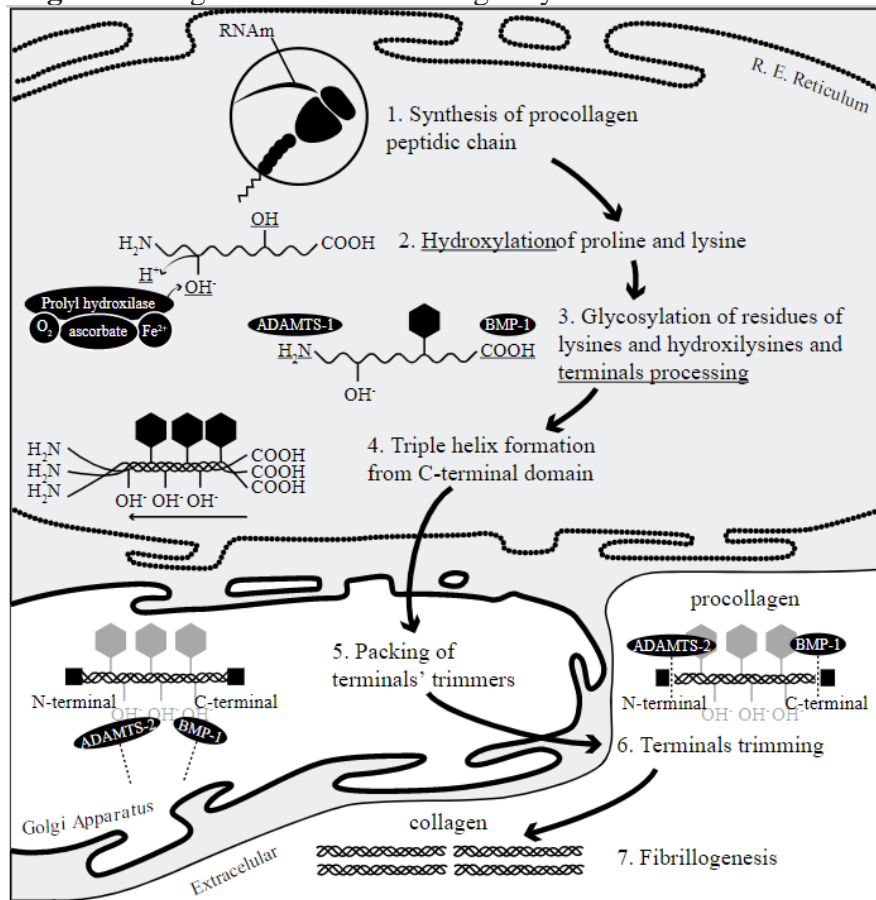
Currently, about 27 forms of collagen are known, but, despite their structural and functional differences, it is notable that, in all these forms, there is a repeated sequence of glycine-YX amino acids in each chain that forms the collagen, originating its helical aspect (Albaugh et al., 2017). The endogenous synthesis of this protein occurs naturally and mainly in two situations, during a healing process or during the tissue formation in the embryonic period (Caliari et al., 2014). This biosynthesis is a very well-regulated process, divided into stages: Transcription of genes and translation of proteins; post-translational modifications; Extracellular secretion of collagen; Extracellular changes and fibril assembly (Chen et al., 2018).

This process begins with the transcription of the collagen mRNA, translated into the rough endoplasmic reticulum of fibroblasts into pro-collagen molecules. In this mRNA

processing, the hydroxylation of the amino acids proline and lysine occurs, forming hydroxyproline and hydroxylsine, which are useful in stabilizing the collagen triple helix (Chen et al., 2018). The proline hydroxylation is performed by the enzyme prolyl-hydroxylase, which requires oxygen, iron and ascorbate to perform its activity (Albaugh et al., 2017). Glucose can bind to lysine and hydroxylisine residues in the glycosylation process, which is important for the structuring of fibrils (Hudson et al., 2018). These pro-collagen molecules are in union with carbon terminal (C-terminus) and amino terminal (N-terminus) globular peptides; the presence of these peptides causes a spatial impediment, so that there is no premature assembly of a collagen fibril (Silva & Pena, 2012)

Each of these peptides is metabolized in a different way and by different enzymes, with the C-terminal peptide being processed by bone morphogenetic protein 1 (BMP-1) or Furins, while the N-terminal peptides are processed by enzymes of the α -disintegrin family. (Mienaltowski & Birk, 2013). Then, the carbon-terminal portions of the 3 alpha chains produced are aligned, initiating the formation of triple helices, which goes towards the amino-terminal portion, which is then sent to the Golgi Complex for the purpose of excretion to the extracellular environment (Chen et al., 2018). The processing of the peptide may be complete, leaving a molecule with a large central triple helix, as in the case of collagen types I and II; however, with collagen III, V and XI, processing may be incomplete, with retention of a telopeptide C and a partially processed N- propeptide domain, which is involved in the modulation of fibrillogenesis (Mienaltowski & Birk, 2013).

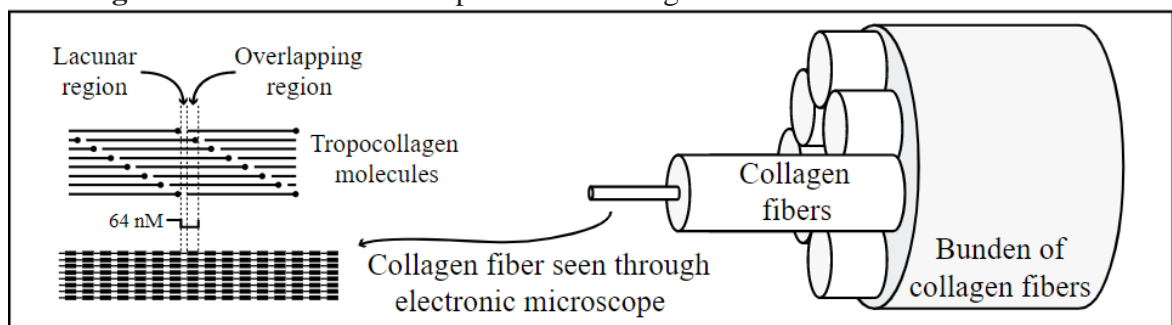
Figure 2. Stages of molecular collagen synthesis.



Source: Authors, 2020.

Collagen fibrils are composed of junctions of collagen molecules along a parallel axis; these can be stabilized by covalent cross-links, providing the necessary mechanical properties to maintain their conformation (Delgado et al., 2017), the set of fibrils form collagen fibers, which organize themselves in the form of bundles.

Figure 3. The structural composition of collagen.



Source: Authors, 2020.

The relationship between collagen and aging

The newly synthesized collagen molds itself into collagen fibrils, which are stabilized through inter and intra-fibrillar cross-linking reactions (Canty & Kadler et al., 2005). Cross-linking reactions can be enzymatic, which usually happen during the process of developing and maturing collagen, and can be non-enzymatic, which happen during the aging process and are harmful to proteins and to associated biomolecules. Often, non-enzymatic changes are the result of glycation reactions, caused due to the accumulation of advanced glycation end products (Wilson et al., 2012). Such non-enzymatic cross-linking reactions interfere with cell-matrix interactions, affecting cell adhesion and dissemination, in addition to decreasing tissue remodeling capacity (Wilson et al., 2012).

However, cross-linked collagen fibrils have a half-life of 15 years (Verzijl et al., 2000), so, after this period, a gradual cleavage of collagen, conducted by extracellular matrix metalloproteinases, occurs during aging. (Li et al., 2015). Under this bias, cleavage has, as a direct consequence, the accumulation of reticulated collagen fragments in the extracellular matrix, due to their resistance to proteolysis (breaking of peptide bonds), thus causing a continuous degradation and disorganization of the ECM, which are extremely harmful processes for the maintenance and longevity of fibroblasts (Fisher et al., 2008). Fibroblasts bind around collagen fibrils to form adhesion sites, which act through the cytoskeleton guaranteeing the execution of contractile forces, thus determining the cytoskeleton morphology and organization (Hegedus et al., 2008). Thus, collagen degradation causes the loss of these adhesion complexes, resulting in a decrease in the spread of fibroblasts, which is observed in the human skin with advancing age (Li et al., 2015).

The glycation reaction is a post-translational modification of the protein, where the attachment, through covalent bonds, of a sugar residue occurs, resulting in the irreversible production of advanced glycation end products, which can form cross-links between the collagen molecules, increasing the intermolecular space (Malik et al., 1996). In addition to the glycation reaction causing the formation of such products, which decrease collagen flexibility, another consequence of this reaction is its contribution to oxidative stress through a spontaneous glycoxidation process, which involves weakening of the collagen. Thus, collagen strength and flexibility are the two main properties of collagen that are dramatically altered during the aging process (Frey et al., 2004).

Li et al., (2015), through their experiments with cell cultures, demonstrated that prostaglandin E2, a pleiotropic lipid synthesized from arachidonic acid through sequential actions of cyclooxygenases (COX-1 and COX-2) and prostaglandins E synthetases (PTGES 1,2 and 3) during the inflammation process, inhibits the collagen production by fibroblasts. During aging, the concentrations of COX-2 and PTGS1 increase progressively, and fibroblasts are the main cellular sources of these two enzymes. Since the spread of fibroblasts/mechanical strength is drastically reduced with advancing age due to the accumulation of fragments of collagen fibers in intercellular spaces, there is an increase in the expression of COX-2 and PTGS1 and PGE2 levels, which are 70% higher in the skin of elderly people in comparison to the PGE2 levels in the skin of young individuals, contributing to the decrease in collagen synthesis.

Cheng et al., (2011) demonstrated, through their studies with skin samples of different age groups, that the levels of collagen types 1 and 3, as well as the proportion of collagen type I/III were altered, as the age advances. The levels of collagen types I and III found in the skin of elderly individuals were about 25% and 40%, respectively, lower than the levels of these types of collagen in the skin of individuals who were in their adolescence. Accordingly, the proportion between type I/III increased by about 30% in comparison to the proportion present in the skin of adolescents. Therefore, the skin of elderly people is more fragile, thin and flabby, in addition to being more susceptible to wounds and imperfect healing processes, since collagen, especially types I and III, has a fundamental role in the process healing tissue formation.

Environmental and genetic factors that can interfere with collagen synthesis

a) Estrogen

Estrogen protects both skin and bones from possible degradation as age advances, by minimizing the decrease in collagen content and bone mineral density, events that occur during aging, especially during the menopause period, being considered, therefore, a great alternative for the successful maintenance of such structures (Verdier-Sévrain et al., 2006).

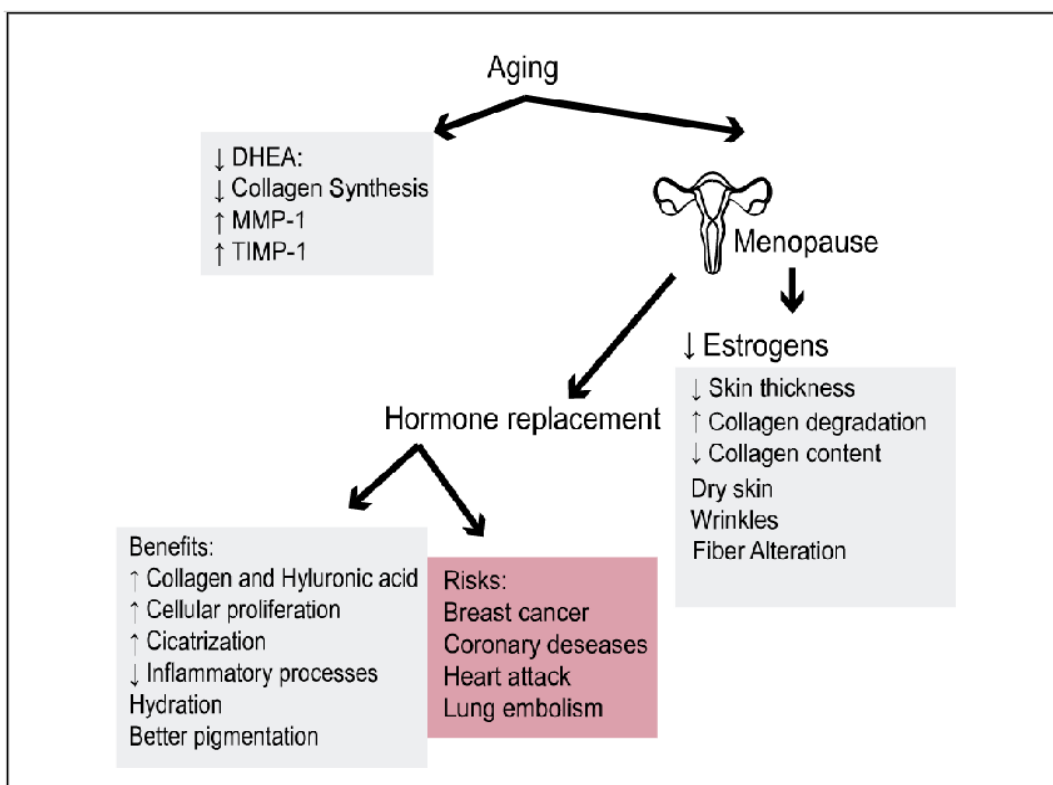
Albright et al., (1941) and, later, Brincat et al., (1987) demonstrated that the type 1 and type 3 collagen content, the proportion between type 3/1 collagen and the skin thickness decreased, and, consequently, there was a decrease in bone mineral density as women

age. Later, Affinito et al., (1999) proved that such decreases were related to menopause, mainly during the first years of this period, due to the decrease in the estrogen content in the female body. Castello-Branco et al., (1992) showed that oral and transdermal hormone replacement therapy for one year led to an increase in collagen content in the skin by 1.8%-5.1%

Callens et al., (1996) pointed out that, through different hormone replacement therapies, there was an increase in skin thickness by 7%-5% in women who are in the menopause period, due to the use of estradiol gel. Also, Maheux et al., (1994), using a test group and a control group, when supplying conjugated estrogen in oral form, noticed a considerable increase in the dermis and, consequently, in the thickness of the skin.

Sauerbronn et al., (2000) showed that, after 6 months of treatment with estradiol valerate and cyproterone acetate in skin samples, there was a 6.9% increase in collagen fibers in the dermis and, later, Varilla et al., (1995) proved that estrogen, in addition to increasing the collagen content in the skin, also increases its synthesis, due to the increase in the levels of procollagen types 1 and 3.

Figure 4. The relationship between collagen and estrogen.



Source: Authors, 2020.

b) Nutrition

The ingestion of a high-calorie diet for a long period increases the chance of incidence and severity of many diseases associated with aging (Tuchweber et al., 1975). Caloric restriction decreases the extent of glycation reactions and accumulation of products from glycooxidation (advanced glycation end products) in tendon collagens (Iqbal et al., 2000), decreasing the damage caused to this protein by such products and thereby increasing the life span of collagen.

A problem related to advancing age is the increased collagen deposition in the heart, especially in the left ventricle, and, through studies with rats presented by Fornieri et al., (1999), it was demonstrated that the rodents that were under a calorie restriction had, in comparison with rodents with a high calorie diet, less degeneration of the arteries and less deposition of collagen in the heart, consequently decreasing the level of fibrosis in the latter with age.

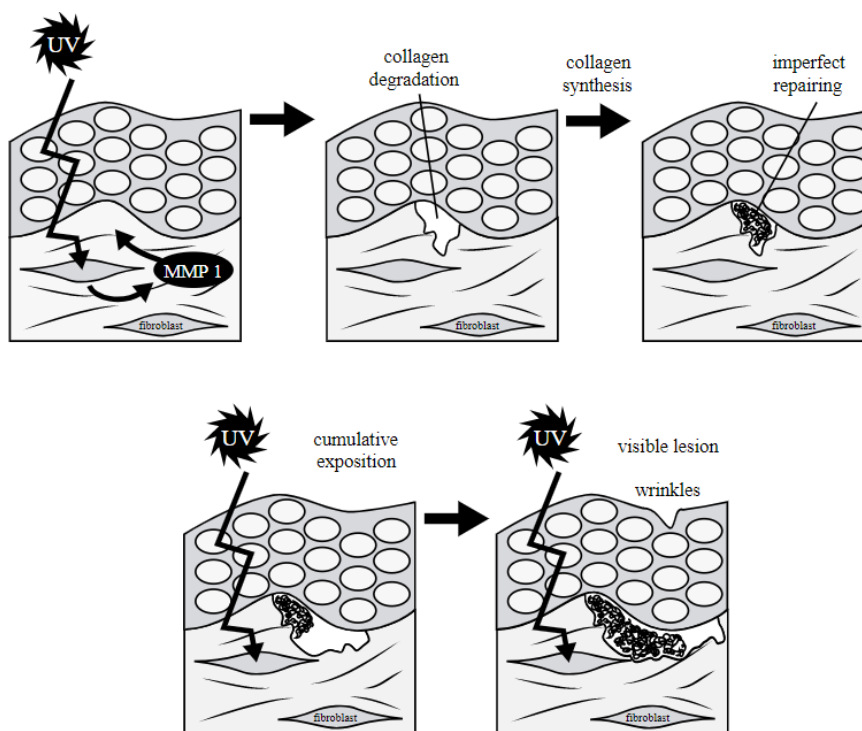
Collagen is a fundamental part of the treatment and healing of deeper wounds, since the healing tissue is mostly composed of collagen. Collagen synthesis and remodeling is the last, most critical and time-consuming step in the wound healing process, which requires other factors to be carried out correctly, such as ATP, oxygen, vitamins, minerals and, especially, amino acids. Therefore, a balanced diet, rich in certain amino acids, mainly glycine, proline and hydroxyproline and capable of providing sufficient energy and essential protein substrates is crucial for collagen synthesis, having, as a direct consequence, a successful wound healing, decreasing the chances of possible complications in the short and long term, such as infections and hernia formation (Albaugh et al., 2017).

c) UV radiation

Ultraviolet radiation upon contact with the dermis stimulates the occurrence of a molecular chain reaction, which results in upregulation (the cell increases the amount of cellular components, such as RNA or proteins in response to an external stimulus) of degenerative matrix metalloproteinases: collagenase (MMP-1), 92 kDa gelatinase (MMP-2), stromelysin (MMP-3) and 72 kDa gelatinase (MMP-9), which are mainly responsible for the degradation of the extracellular matrix (Lahmann et al., 2001). Together, such metalloproteinases are able to fully degrade collagen; MMP-1 is able to damage intact

collagen fibers, while the other MMPs are able to degrade damaged collagen fragments (Freitas-Rodríguez et al., 2017), drastically and negatively affecting the performance and cellular function of this protein. Trying to repair such degradations, collagen synthesis occurs; however, the newly synthesized collagen cannot repair it perfectly such damage, forming flaws/scars that are not visible to the naked eye. However, after repeated cycles of exposure to the sun, such flaws are accumulated and become visible to the naked eye as wrinkles and sagging spots on the skin (Farage et al., 2008).

Figure 5. Interference of UV radiation on collagen.



Source: Authors, 2020.

d) GH / IGF-1

GH and type 1 insulin-like growth factor are essential for the structural maintenance of proteins, for example, collagen, of ligament and of tendons (Vestergaard et al., 2012). However, with advancing age, GH secretion levels and IGF-1 bioavailability decrease dramatically, making such structures more susceptible to damage. Hansen et

al., (2012) demonstrated that local injections of IGF-1 in the patellar tendon of healthy elderly individuals increase the synthesis of collagen in the tendon. In addition, Vestergaard et al., (2012) conducted an experiment with 12 healthy elderly men to examine whether rhGH injections would increase the synthesis of collagen in the patellar tendon, where a saline injection (placebo) would be injected into the patellar tendon of one of the legs, while, in the other leg, an injection with rhGH would be administered. It was observed that, in the leg of 10 of the 12 elderly people, there was an increase in the collagen synthesis in the patellar tendon, in addition to also stimulating the local synthesis of IGF-1, instead of having it released by the liver.

e) Tobacco extract smoke

Studies have shown that tobacco extract smoke induces the expression of metalloproteinases, especially types 1 and 3, which act on collagen degradation, and do not alter the expression of metalloproteinase inhibiting tissues (TIMPs), thereby causing a change in the MMPs/TIMPs ratio, which favors the formation of a favorable environment for degradation and continuous loss of collagen in the skin (Yin et al., 2000).

Knuutinen et al., (2002), through an experiment with 98 men, 47 of whom were smokers and 51 non-smokers, demonstrated that the levels of MMP-1 and MMP-8, the main metalloproteinases that act in the degradation of collagen types 1, 2, 3 and 5 (Freitas-Rodríguez et al., 2017), were significantly higher in the blood circulation of the skin of smokers compared to those of non-smokers; in addition to that, the concentration of the tissue inhibitors of metalloproteinases (TIMPs) in the blood circulation are 14% lower in smokers. Therefore, due to the increase in metalloproteinases and the decrease in their tissue's inhibitors, the collagen biosynthesis by fibroblasts, mainly types 1 and 3, is drastically reduced, having, as a direct consequence, an increased susceptibility of the skin to long-term deterioration, in addition to contributing to the premature aging of the skin and the formation of wrinkles.

f) Mutations

Mutations in genes that encode the most diverse types of collagen cause skeletal dysplasias, which are characterized by changes in linear growth, bone fragility, severe fractures, joint instability, among other clinical manifestations. Mutations in the COL1A1

gene, which encodes type 1 collagen, cause a decrease in the quality and structural quantity of bones, and increase the chances of bone fracture. Osteogenesis Imperfecta is the main disease (autosomal dominant) resulting from this genetic alteration, characterized by fractures, which are less and less recurrent in the less severe form of the disease (type I), decreased muscle mass and strength, in addition to joint instability. However, type II is lethal in newborns, due to severe fractures and skeletal deformations, such as bone curvature and the development of kyphoscoliosis (Lim et al., 2017).

Mutations in the COL2A1 gene, which encodes type 2 collagen, affect limb ossification centers, height, and cause spinal deformities. Therefore, individuals with these mutations have short stature, associated with vision and hearing problems, and, in some more severe cases, such as Achondrogenesis type 2, it can lead to respiratory failure, because, in addition to the individual having extremely short limbs and ribs, their lungs are smaller and their thorax has not been fully developed (Chen et al., 2018).

Mutations in the COL3A1 gene, which encodes type 3 collagen, result in a decrease in the amount of type 3 collagen, which can cause the development of the vascular form of Ehler-Danlos syndrome, in which patients have joint instability, increased risk of muscles and tendons ruptures, and, in some cases, rupture of arteries. Mutations in the COL5A1 and COL5A2 gene, which encode type 5 collagen, result in the classic form of Ehler-Danlos Syndrome, in which patients have cutaneous hyperextensibility, joint instability with subsequent complications, such as sprains, dislocations and pain. The diagnosis of these genetic collagen disorders is done through exome sequencing (WES-whole exome sequencing), since exons are the functional part of DNA (about 2% of the entire genome), thereby substantially reducing the time and cost of diagnoses when compared to sequencing the entire genome (Chen et al., 2018).

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