Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181

e-ISSN: 2321-6212
p-ISSN: 2347-2278

Materials Science and Mechanics of Collagenous Tissues

Frederick H Silver[1*] and Dale DeVore[2]

[1]Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School, Rutgers, the State University of New Jersey, Piscataway, NJ, USA

[2]DV Consulting Services, 3 Warwick Drive, Chelmsford, MA, USA

Research Article

Received: 23/05/2017
Accepted: 18/07/2017
Published: 25/07/2017

***For Correspondence**

Frederick H. Silver, Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School, Rutgers, the State University of New Jersey, Piscataway, NJ, USA, Tel: +6104282173.

Email: fhsilver@hotmail.com

Keywords: Collagen, Viscoelasticity, Mechanical properties, Modulus, Skin, Tendon, Bone

ABSTRACT

Collagen is the major structural protein found in mammalian extracellular matrix (ECM). ECMs act as biological mechanotransducers that prevent premature mechanical failure of tissues, store and transmit energy created by muscular deformation, and amplify protein synthesis and cell division as the applied stress and loads are increased (mechanochemical transduction). Fibrous collagens play important roles in health and disease processes much of which depends on the mechanical properties of these tissues. The purpose of this paper is to summarize our knowledge of relationship between the structure and mechanical properties of fibrous collagens in vertebrates.

INTRODUCTION

Collagen is the most abundant protein found in the extracellular matrix (ECM) of vertebrates. It forms the fibrous backbone or parenchyma of many tissues, the support for cells at tissue interfaces, and is the primary structural component of the musculoskeletal system. The collagen family is composed of several collagen subfamilies including fibril forming collagens, beaded filaments, anchoring fibrils and network forming collagens [1]. The structural stability of tissues is the result of the formation of collagen fibrils, fibril bundles, fibers and fascicles in tendon, and in other tissues collagen fibrils and fibers are the structural components. Most collagen fibrils are composites since they are made up of more than one collagen types such as tendon (types I, II and V), cartilage (types II, IX and XI), skin (types I and III) and cornea (types I, III and V). In addition, other non-collagenous macromolecules are attached to collagen fibrils that are involved in fibril formation (proteoglycans), cell-collagen interactions (fibronectin) and mechanotransduction (integrins) [1]. The purpose of this paper is to relate the structural hierarchy of collagen fibrils and fibers to the mechanical behavior of collagenous tissues to help better understand the function of collagen in health and disease.

Mechanical and Metabolic Roles of Collagen in Tissues

Collagen fibers in vertebrate extracellular matrix (ECM) serve important mechanical roles including preventing premature mechanical failure and modulation of force transfer between neighboring tissues [2,3]. They store elastic energy during muscular deformation, transmit stored energy resulting in joint movement, transfer excess energy from the joint back to the attached muscles for dissipation and promote regulation of cell and tissue synthesis through a process known as mechanochemical transduction [4]. They act as mechanotransducers by transferring stress borne by the musculoskeleton and other tissues to the attached cells in order and regulate tissue metabolism, either up- or down, as a result of changes in mechanical loading [3]. Collagen fibers transduce mechanical loading into changes in chemical synthesis of proteins which leads to energy storage in the form of high

e-ISSN: 2321-6212
p-ISSN: 2347-2278

molecular weight proteins (mechanochemical transduction). Therefore, collagen fibril and fiber structure is intimately related to: energy storage, transmission, dissipation, premature mechanical failure of tissues, and up- and down-regulation of tissue metabolism. Changes in collagen structure have been noted in diseases such as cancer, scarring, osteoarthritis and inflammation suggesting that collagen structural changes may be a useful parameter to follow in the early diagnosis of these diseases.

Location and Function of Collagenous Tissues in Vertebrates

Collagen fibrils and fibers are found in a variety of tissues throughout the body. They can be found in both unmineralized and mineralized tissues and can be classified into the following categories: (1) surface and internal lining tissues, (2) conduit and holding structures, (3) parenchymal or organ-supporting tissues, and (4) dental and musculoskeletal tissues [5].

The ECM of surface and internal linings is composed of collagen, proteoglycans, elastin, glycoproteins, cells and water and is found in internal and external lining structures at the interfaces with the air or internal tissue [5]. Examples of these include cornea, skin, alveoli, oral mucosa, vagina, and uterus. These sheet-like tissues provide mechanical, chemical, and microbiological barriers to keep what is in the environment from penetrating into host tissue **(Figure 1)**. The internal linings such as pleural and peritoneal membranes protect organs in the thoracic and abdominal cavities from injury. Collagen fibrils and fibers in this class of tissues are found as networks that can be considered planar reinforcement elements that provide mechanical support but they also are involved in mechanotransduction as described below [3]. Skin and cornea are examples of surface and internal lining structures and contain surface cellular layers that cover collagenous supporting layers.

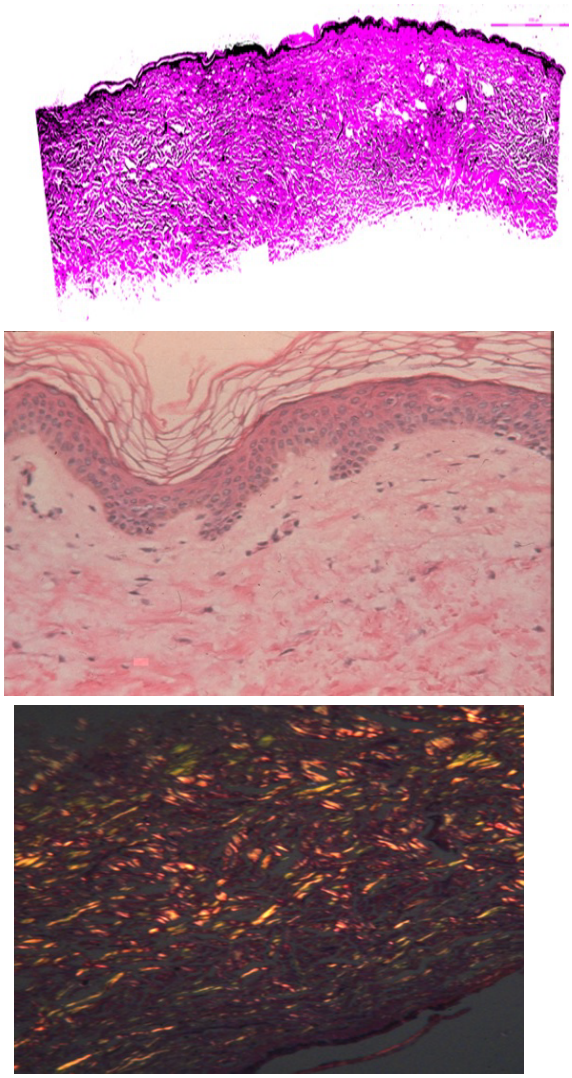

Figure 1. Histolological images of skin, an example of a surface and internal lining structure. (Top) Montage of images obtained from histologic cross-sections of human skin reconstructed using an image analysis program. The dark layer on top is the epidermis that is composed of dead keratinized cells. The pink material in the majority of the section is composed of collagen fibers. (Middle) High magnification view of the surface of skin showing: (1) dead keratinized layers on surface appearing to slough off; (2) a series of between seven and ten cellular layers with round to ellipsoid shapes that make up the epidermis; and (3) the pink collagenous fibers that support skin that are found in the dermis. The dark elongated nuclei of cells found between the collagen fibers are predominantly fibroblasts. (Bottom) This micrograph, taken under polarized light, shows the biaxial orientation of collagen fibers within the cross-section of skin. These collagen fibers align with the tensile direction during mechanical loading and prevent mechanical failure of the skin. Collagen fibers in the dermis are round to ellipsoid in shape when skin is sectioned either parallel to the surface or in cross-section.

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

A second classification of tissues includes conduit and holding structures, which are tubes and containers with three or more layers that make up the walls. For example, blood vessels **(Figure 2)** contain an intima or cellular layer in contact with the flowing blood, a muscular or medial layer, and an outer layer termed adventitia that blends with the surrounding tissues. Other tubular structures are similar in that they consist of an internal cellular layer (mucosa), surrounded by a muscular layer (muscularis), and an external ECM containing layer (serosa). Collagen fibrils and fibers in these tissues are mixed with elastic tissue and smooth muscle cells and serve to reinforce the tissue walls [5].

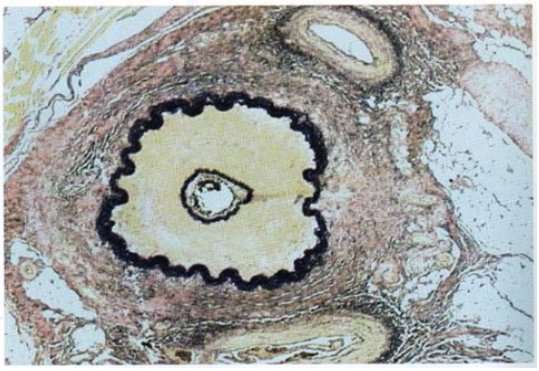

Figure 2. Example of the morphology of a conduit and holding structure. Histological section of a pig femoral artery stained with Van Giesen's stain and counterstained with eosin. Note the artery in the micrograph is filled with protein trapped in the center. The dark rings are composed of elastic fibers (media) that sit on a very thin layer of cells termed the intima that is too small to be seen in this micrograph. The adventitia surrounds the media and blends into the tissue surrounding the vessel wall. Pink collagen fibers make up the bulk of the adventitial layer.

Parenchyma and organ supporting collagens form the scaffold of major organs such as liver, kidney, heart and lymph nodes [5]. The collagen fibrils and fibers in these tissues support cells and in conjunction with other tissue elements allow cell-based physiologic processes to occur within a fixed organization of cells. In liver, the collagen fibrils support the endothelial cells that line the sinusoids allowing large quantities of blood to be filtered.

The last classification of tissues is dental and musculoskeletal tissues. These tissues include anterior cruciate and other ligaments, spongy and dense long bones, periodontal ligament, tendons, and intervertebral disc of the back [5]. The collagen fibrils and fibers of these tissues provide structural stability in the presence and absence of mineral termed hydroxyapaptite **(Figure 3)**.

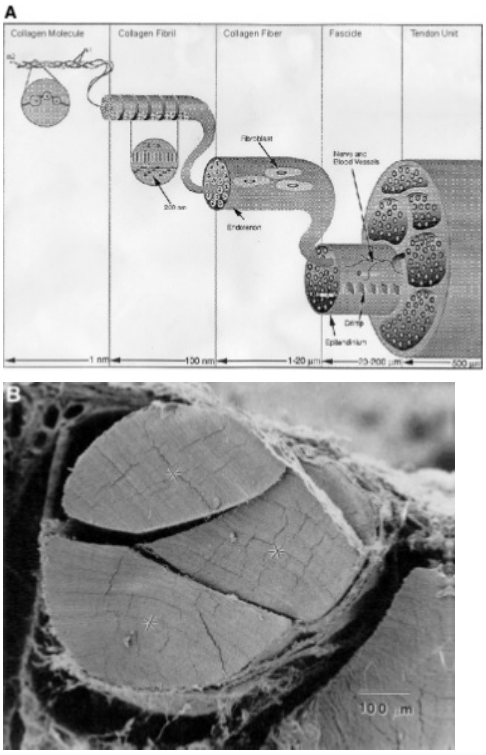

Figure 3. Example of dental and musculoskeletal structures. Structural hierarchy in the tendon. (A) This diagram illustrates the relationship between collagen molecules, fibrils, fibers, fascicles, and tendon units. Although the diagram does not show fibril subunits, collagen fibrils appear to be self-assembled from intermediates integrated within the fibril termed microfibrils. (B) Scanning electron micrograph of a rat-tail tendon fiber showing the fascicles (see asterisks) that make up the tendon unit. The tendon unit is composed of collagen fibrils, fibers and fascicles. Collagen and skeletal muscle fascicles are found primarily in musculoskeletal tissues.

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

Thus fibrous collagen is found in almost every tissue and organ in vertebrates. Collagen fibers are composed of collagen triple-helical molecules that are derived from one or more of the 28 collagen types that compose the collagen family [1]. While we will concentrate on fibrous collagens in this paper, the collagens of the other subfamilies plays additional roles in mammalian tissue structure and function.

Collagen Molecular Structure

All collagens contain amino acid sequences of gly-X-Y where X and Y are frequently proline and hydroxyproline. The sequence gly-X-Y leads to the formation of a left-handed triple helix and three left handed triple-helices form a right handed superhelix. The length of the triple helical segments varies between collagen sub-families with the longest triple-helical segments found in the fibril forming collagens that have about 1000 amino acids in a single left handed helix.

In the fiber forming collagens, this three chained molecule forms a right-handed triple helical structure containing glycine residues buried at the center of the cylindrical molecule and is synthesized in a longer precursor form termed procollagen **(Figure 4)**. The most abundant subfamily is the fibrillar collagens of which type I collagen is found in tendons, skin, cornea, bone lung and vessel walls [6]. This collagen is thought to give rise to the high tensile strength of collagen fibers in tendon; in addition, it actively is in\

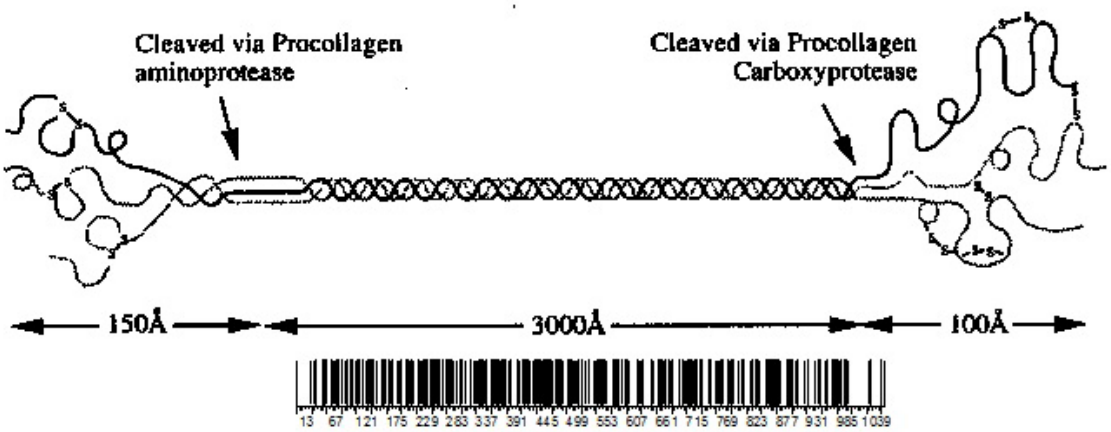

Figure 4. Diagram showing the structure of procollagen, the biosynthetic precursor of the collagen molecule. Procollagen molecules are formed within the cell and the large propeptides on the ends of the molecule are extracellularly cleaved during self-assembly into collagen fibers. Collagen molecules are triple helical rods about 300 nm in length as shown by the arrows in the diagram. The flexibility profile is shown below the diagram of the collagen triple helix and the 300 nm (3000 Angstroms) line that represents the triple helical portion. The dark vertical lines represent rigid regions and the light areas depict the flexible domains of the collagen triple helix at the bottom of the figure. The amino acid residue numbers along the axis of the triple helical collagen molecule are shown at the bottom of the flexibility profile. Note that the collagen triple helix is a composite of flexible and rigid regions. The flexible regions do not contain the imino acids proline and hydroxyproline and they are the first regions to deform reversibly under a tensile load during stretching of the triple helix.

Collagen synthesis from amino acids begins on the ribosomes within the cell cytoplasm; the synthesized chain is then folded into a triple helix after hydroxylation of proline is completed. The molecules are then transported through the Golgi apparatus, packaged into vesicles, and then are added to growing fibrils in recesses within the cell membrane. However, collagen fibrils are not mechanically stabilized until they are crosslinked which occurs after release from the cell and mechanical loading begins [7,8].

Procollagen triple helices contain extra pieces on the C and N terminal ends of the molecule termed propeptides **(Figure 4)**. The propeptides are removed sequentially during collagen assembly. Collagen triple helices, 1.5 nm wide and 300 nm long, are packed into a “quarter-staggered” packing pattern that results in nearest neighboring molecules being staggered longitudinally by about 22% of their molecular lengths with a space or hole between the head of one molecule and the tail of the next **(Figure 5)**. Early studies recognized that five collagen molecules were packed in a staggered fashion to form a microfibril [9,10] that was identified by electron microscopy [11]. It is now believed that collagen molecules are packed laterally into quarter-staggered quasi-hexagonal units that are in turn longitudinally packed into microfibrils. Collagen microfibrils are believed to be continuous and run the length of a tissue; they are fused laterally into fibrils and fibers in most tissues [7,8,12,13].

In the 1970s collagen molecule was thought to be a rigid rod based on the observation that the translational diffusion constant was 0.86×10^{-6} cm^2/sec, which was very close to that calculated for a prolate ellipsoid 1.5 nm wide and 300 nm long [14]. However, later measurements, based on rotary shadowed images of collagen molecules, suggested that the molecules had numerous bends as shown in **Figure 6a** [12]. Analysis of the molecular sequence of type I, II and III collagens suggested that the flexibility of the collagen triple helix arises from areas in the sequence that are devoid of proline and hyroxyproline, two imino acids that constrain rotation and flexibility of the molecule [13] **(Figure 5)**. Further analysis suggested that these flexible regions are preserved when the molecules are packed into a quasi-hexagonal packing pattern indicating that flexibility is an important aspect of the collagen fibril structure [13].

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

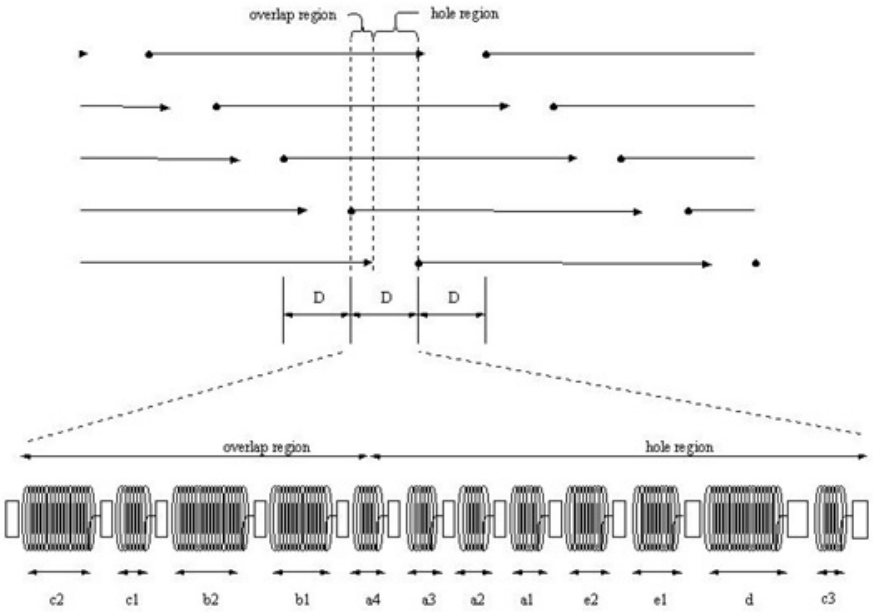

Figure 5. Diagram of quarter-staggered packing pattern of collagen molecules in collagen fibrils in two dimensions. In the quarter-stagger packing pattern, collagen molecules, 4.4D long, are staggered with respect to their neighbors. In tendon, the collagen molecules are shifted with respect to each other by a distance D equal to 67 nm. When collagen molecules are stained with metal ions and then viewed in the electron microscope, a series of light and dark bands are observed across the axis of the fibril and are designated b2, b1, a4, a3, a2, a1, e2, e1, d, c2 and c1. The distance D is made up of a hole region of about 0.6 D and an overlap region of about 0.4 D. The D period is the characteristic fingerprint of fibrous collagen. The bands in the D period are enlarged at the bottom and the flexible charged regions are denoted by springs while the rigid regions are depicted by cylinders. The springs shown are identical to the light regions shown at the bottom of **Figure 4**. When collagen is stretched in tension the triple helix elongates and the D period increases. The increase in the D period is reversible and is the basis of the energy storing ability of the collagen fibers. Note this energy storing ability requires cross-links that are formed between neighboring molecules that are staggered by 4D at sites shown by circles and arrows in the diagram.

Supramolecular Structure of Collagen

Collagen in tissues is recognized by transmission microscopy by its regular repeat of the charged amino acid residues. In the quarter-staggered packing pattern, the amino acid sequence of the five molecules in cross-section is repeated every 64 to 67 nm, a distance termed the D period **(Figure 5)**. The positively stained sub-bands in the D period (see **Figure 6**) can be depicted as spring-like **(see Figure 5)** and can be directly visualized by staining with heavy metals **(Figure 6)**. The D period varies from about 64 to 67 nm depending on the tissue of origin. In tendon, the D period is about 64 nm and in skin it is about 67 nm **(Figures 6 c-e)** . At the light microscopic level, collagen fibers in tendon are distinguished from other tissue proteins by the cross striated pattern derived from the crimp seen under polarized light **(Figure 6k)**. Other tissues contain collagen fibers in aligned (tendon) and oriented networks (skin) that are visualized under polarized light.

For instance in tendon, collagen fibril diameters are between 20 and 280 nm and collagen fibers diameters are between 1 and 300 μm [13]. While collagen fibrils form from lateral addition of smaller fibrils, they form bundles of fibrils and larger bundles termed fascicles as shown in **Figure 3**. Groups of fibril bundles form fascicles that in turn make up the cross-section of a tendon bundle **(Figure 3)**. These structural elements acting in concert give rise to the mechanical properties of tendon and allow structures such as the finger joints to bend independently.

The ultrastructure of tendon has been studied extensively as a function of maturation. Collagen microfibrils appeared to be held together by an interfibrillar matrix containing proteoglycans. These collagen fibrils were observed to have a planar waveform, termed crimp, and be the load bearing units [15] **(Figure 6k)**. Upon deformation, the stress-strain curve of tendon curves upward after the crimp is removed [15]. After birth, the distribution of fibril diameters from rat tail tendons is fairly flat supporting the concept that fibril diameter and length increases occur by the lateral fusion of fibril bundles [7,8,12,16,17]. The volume fraction of collagen fibrils increases during maturation until it reaches about 0.5; in fibril cross-sections of tendon small collagen fibrils fill the space between larger ones [16].

Collagen Crosslinking

The ability of fibril forming collagens to store, transmit and dissipate energy requires crosslink formation between molecules within a microfibril and between microfibrils and other structural units [3] as indicated in **Figure 5**. These crosslinks include lysine and hydroxylysine derivatives and other amino acid residues including histidine [3,18]. Crosslinking also occurs during aging and involves glucose molecules [1]. The stiffening and poor energy dissipation of collagen fibers associated with aging probably involves collagen fiber fragmentation by UV light and glucose derived crosslinking. This leads to loss of the energy dissipating ability of extracellular matrix and is associated with large energy losses during pulsatile blood flow in the cardiovascular system [19].

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

Viscoelastic Behavior of Collagen Fibers

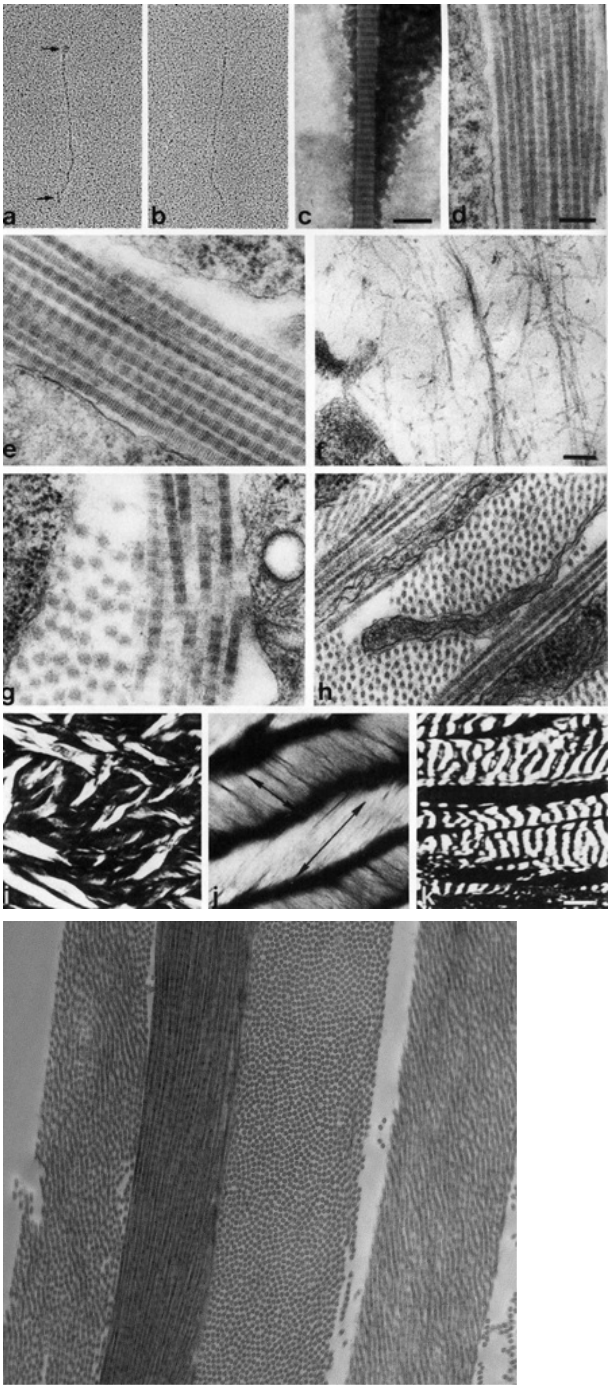

Figure 6. Structural hierarchy of collagen in ECMs. (Top) Collagen molecules are semi-flexible rods (see bends in 6a, b), that form cross-striated fibrils in tissues with repeat periods between 64 and 67 nm 6 c-e) or filamentous structures (6f). Collagen fibrils are formed in deep recesses of the cell membrane (6g,h) and under polarized light appear as planar biaxial structures in dermis) (6i), orthogonal structures in bone (see arrows for collagen molecular directions in 6 j) and crimped planar waveforms in tendon (6k). This figure was modified from Birk et al. [12]. The non-linear viscoelastic behavior of collagen fibers is due to geometrical orientation of the collagen fibers and the presence of other components (Bottom) Collagen fibrils in cornea. Transmission electron micrograph illustrating the arrangement of collagen fibrils that is present in the cornea. This micrograph illustrates that collagen fibrils in cornea form sheets with a preferred direction; the direction of the collagen fibrils changes from sheet to sheet. The transparency of the cornea requires that the diameters of the fibrils be small compared to the wavelength of light. Collagen fibrils in skin and tendon are much larger since these tissues are not required to be transparent.

Collagen fibers are viscoelastic and exhibit time-dependent mechanical behavior **(Figure 7)**. Viscoelasticity may be important in resisting impact loads at low strain-rates especially in the musculoskeleton, however, it complicates the understanding of ECM behavior since most real-time measurements made on these tissues contain both elastic and viscous contributions [2]. The elastic behavior varies from as high as about 75% of the total stress for tendon to as low as about 50% for skin depending on the collagen fiber orientation, rate of loading and the quantity of other tissue constituents [2]. Results of recent studies suggest that the elastic modulus of collagenous tissues can be measured by measuring the resonant frequency of a tissue using optical coherence tomography and vibrational analysis which can be done non-invasively and non-destructively [20,21].

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

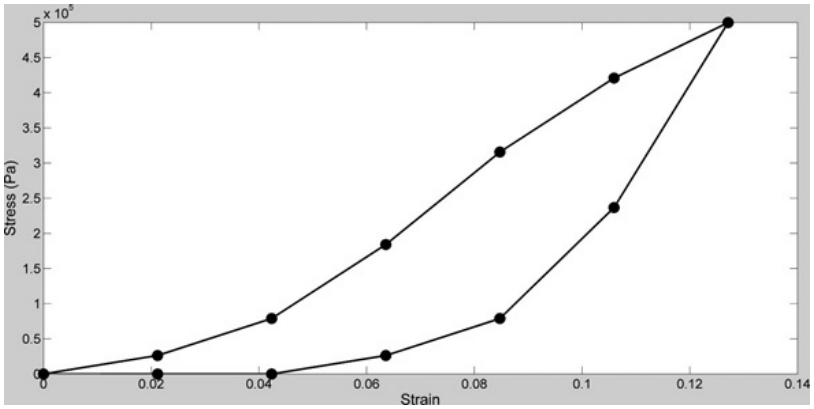

Figure 7. Typical stress-strain curve for decellularized human dermis tested in uniaxial tension illustrating the viscoelasticity and time dependence of the return to zero stress and strain after unloading. The dermis is loaded in tension in strain increments and the force at each strain is recorded before another strain increment is added. The loading curve is above the unloading curve and the sample returns to zero stress and zero strain after a recovery period of about 30 minutes. Non-linearity is a result of several factors including fiber orientation, loading of other components at low strains (elastic fibers) and viscoelasticity. This figure was adapted based on Shah et al. [20].

Role of Collagen in Energy Storage, Transmission and Dissipation

Energy storage, transmission and dissipation are some of the many key mechanical functions provided by fiber forming collagens of the ECM found in vertebrate tissues. These functions are required for effective locomotion, tissue regeneration and repair through mechanotransduction processes [3]. The above mechanical functions are required for vertebrates to achieve locomotion and move efficiently. Vertebrates must be able to develop muscular forces, store elastic energy, and transfer this energy to the attached joints for locomotion to occur. In addition, excess energy remaining after movement is achieved must be transferred from the joint back to the muscles where it can be dissipated as heat [3]. It is important to examine at the molecular and tissue levels how energy storage, transmission and dissipation occur.

Mechanistically, during mechanical loading of tendon it has been shown that a tensional increase in the D period is observed with increasing strain that is associated with: (1) molecular elongation at the triple-helical level of structure; (2) increases in the gap distance between the end of one triple-helix and the start of the next one in the microfibril; and (3) molecular slippage [22]. Molecular stretching occurs at lower stresses followed by increases in the gap spacing **(Figure 5)** and molecular sliding; the latter occur at higher stresses [23].

A molecular modeling program has been used to calculate the change in free energy associated with a 1-3% increase in the h spacing of a type I collagen triple helix packed into a five-membered unit. The resulting free energy calculation was compared to the change in energy under the molecular stress versus strain curve. From these considerations it was determined that changes in free energy during stretching a collagen microfibril were proportional to the energy changes under the molecular stress-strain curve [24]. Furthermore, the regions without imino acids appear to “open up” or uncoil when stress is applied. They appear to serve as sites that can store energy elastically. Peterlini et al. [25] have predicted that these regions can form folds in the collagen triple helix; the folds may unfold when stress is applied and energy is stored. Molecular modeling results suggest that stretching increases steric energy of the triple helix that is attributable to van der Waals and electrostatic interactions between amino acids that are charged [24].

Mechanotransduction and Mechanochemical Transduction

ECMs modulate internal mechanical forces into changes in biochemical signals in a series of phosphorylation events in a process termed mechanotransduction [3]. If proteins and new high molecular weight tissue are formed this process becomes mechanochemical transduction. An example of this process may be described by lifting weights repeatedly for several months. In this situation both the force generated by the muscle increases (mechanotransduction) and the size of the muscles and the amount of skin increase (mechanochemical transduction) [3,13]. These changes occur because many of the ECMs in the human body are under internal tension. The need to balance external forces resulting from lifting weights and the internal forces exhibited by the collagen networks and the resident cells drives mechanochemical transduction [3]. Alteration of the balance between external and internal mechanical forces acting on resident cells found in ECMs, leads to changes in gene expression and subsequent production of ECM proteins [3]. In contrast to tissue stimulation by weight lifting, prolonged bed rest and a reduction in external mechanical loading results in tissue catabolism. This leads to loss of muscle and atrophy of the musculoskeletal system [3]. Therefore any changes in the equilibrium between external and internal mechanical forces acting on ECMs lead to changes in mechanochemical transduction at the cellular level. These changes appear to be important mechanisms by which mammals adjust their needs to store, transmit and dissipate energy that is required for bodily movements in a gravitational field [3].

Mechanochemical transduction is an important process that results in changes in ECM hierarchical structure in both health

e-ISSN: 2321-6212
p-ISSN: 2347-2278

and disease. Therefore, the relationship between mechanical behavior and hierarchical structure must be considered in more detail. **Figure 8** summarizes some of the steps that are involved in converting mechanical loading into changes in tissue structure.

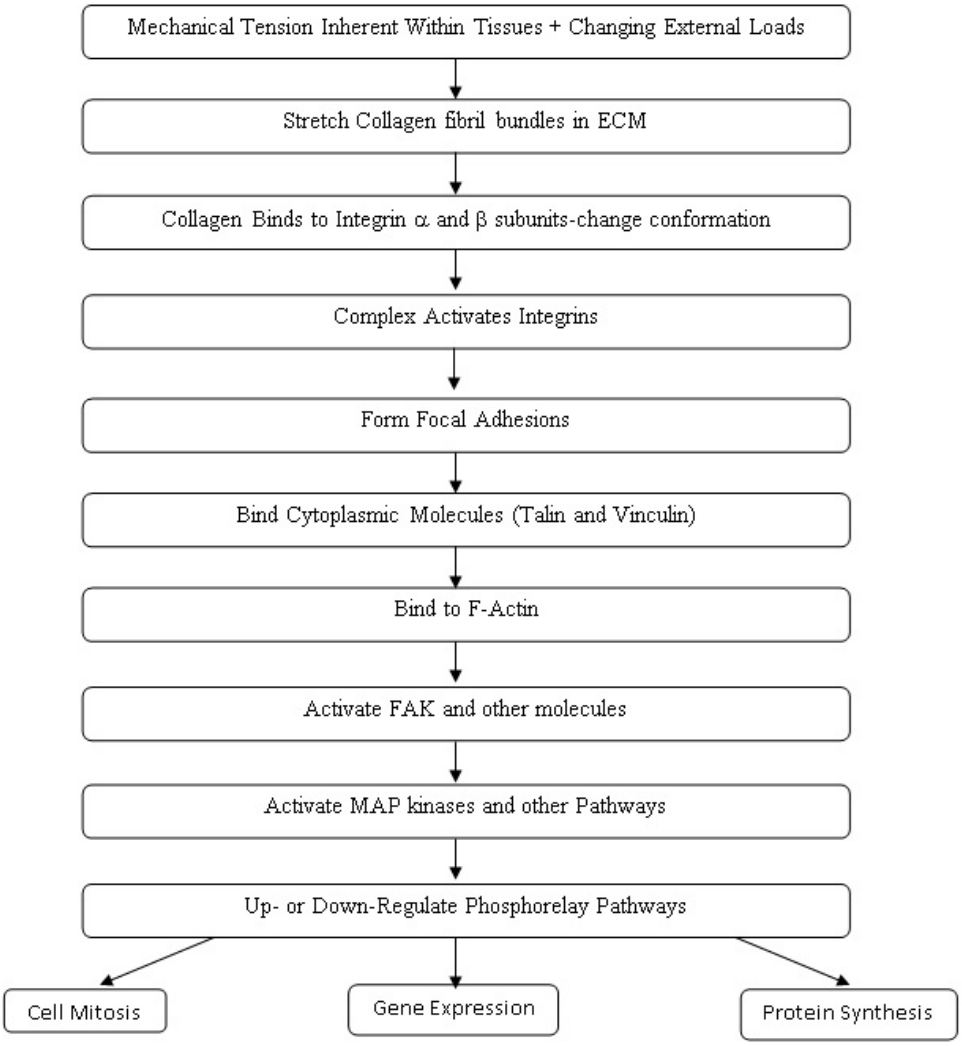

Figure 8. Diagram illustrating how mechanical tension exerted in tissues, such as the tension in Langer's lines in the skin, affects cellular behavior through activation of the phosphorelay pathways. Integrin and non-integrin dependent pathways are involved in activating or deactivating protein synthesis and gene expression because of changes in the mechanical loading experienced by the ECM. In integrin dependent mechanotransduction, tension in collagen fibers causes a conformational change in the integrin subunits that are attached to specific bands on the collagen fibrils. This causes formation of focal adhesions, binding of talin, other intracellular molecules including F-actin. This leads to activation of FAK in the cytoplasm followed by activation of MAP kinase pathways leading to alteration of protein synthesis and gene expression. For example, increased muscular work by weight lifting, or mechanical forces on the palm of the hand associated with pounding a hammer, cause skin cells to up-regulate protein synthesis and cell mitosis. This causes more skin covering the muscles and thicker skin on the palm of the hands, respectively when these tissues are loaded in tension.

Non-Invasive and Non-Destructive Methods to Determine the Mechanical Properties of Tissues

The ability to monitor the mechanical properties of collagen and ECMs *in vivo* is an important measurement needed for early diagnosis of disease and the ability to follow disease progression. For over 100 years physicians have been able to "palpate" changes in the properties of tissues associated with tumors and calcification; this suggests that there are major changes in the structure and properties of collagen and ECMs during disease processes. It is essential that clinicians be able to assess the changes at the collagen fibril and fiber levels of structure to accurately diagnose and treat diseases such as cancer and osteoarthritis. Several new methods have been developed to try and discern these changes early in the disease process. It is essential that these methods be validated so that the properties measured have some meaning.

We have reported [20,21] the use of vibrational analysis in concert with optical coherence tomography (OCT) to measure the resonant frequency and modulus of a number of tissues. The resonant frequency measured is directly related with the tensile modulus obtained from an incremental stress-strain experiment **(Figure 9)**. The method was recently extended to measuring the modulus of normal skin and scar tissue *in vivo* [21].

Research & Reviews: Journal of Material Sciences
DOI: 10.4172/2321-6212.1000181
e-ISSN: 2321-6212
p-ISSN: 2347-2278

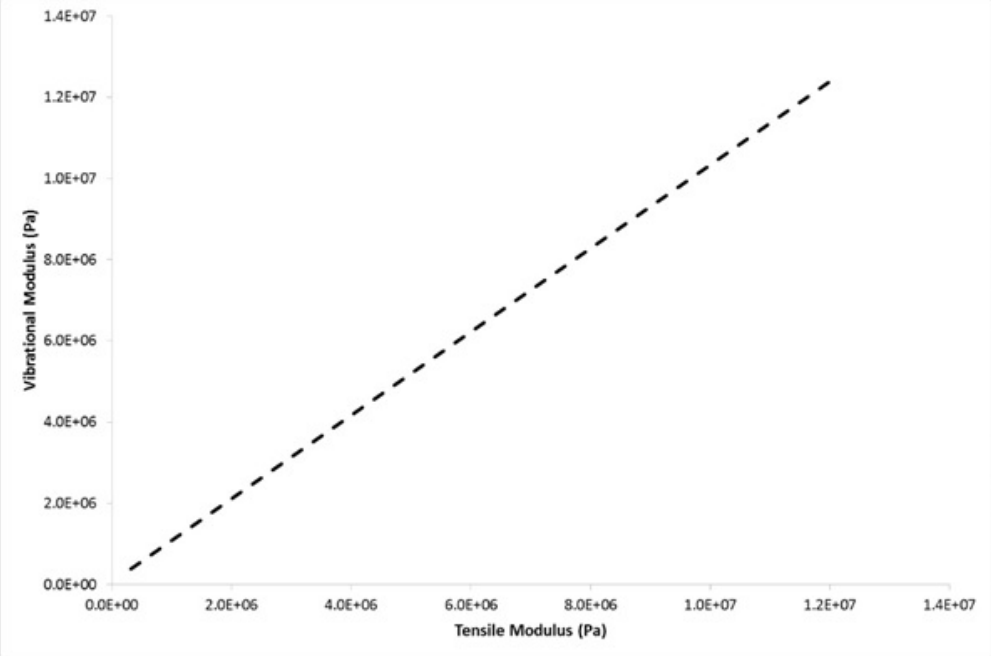

Figure 9. Plot of modulus determined from vibrational studies versus modulus determined from tensile incremental stress-strain testing. The calibration curve shown was modified from Shah et al. [21]. Note the slope is approximately 1.0.

CONCLUSIONS

Collagen is the major structural protein found in mammalian ECMs. It is found in a number of different forms and is important in the structural stability of tissues. ECMs act as biological mechanotransducers that prevent premature mechanical failure of tissues. ECMs store and transmit energy created by muscular deformation and amplify protein synthesis and cell division as the applied stress and loads are increased (mechanochemical transduction). They regulate their size and shape as a result of changing local mechanical demands to tissues. Changes in tissue metabolism are transduced into increases or decreases in synthesis and catabolism of the components of ECMs. In synthesizing high molecular weight macromolecules, energy is stored in the form of covalent bonds. This energy can be released by tissue catabolism if needed.

Energy storage and elastic behavior primarily involve the stretching of flexible regions devoid of imino acid residues within collagen triple helices found in crosslinked collagen fibrils. Since tissue architecture varies among different ECMs so too does the amount of energy that can be stored and dissipated.

It is now possible to evaluate structure-properties relationships for ECMs *in vivo* using OCT and vibrational analysis. This enables clinicians to "quantitatively palpate" tissues to elucidate the relationship between structure and properties in both health and disease.

REFERENCES

1. Ricard-Blum S. The collagen family. Hynes R, Yamada K (eds.) Cold Spring Harbor Pers Biol 2011;1-19.
2. Dunn MG and Silver FH. Viscoelastic behavior of human connective tissue: relative contribution of viscous and elastic components. Connect Tissue Res 1983;12:59-70.
3. Silver FH. Mechanosensing and Mechanochemical Transduction in Extracellular Matrix, Biological, Chemical, Engineering and Physiological Aspects, Springer, New York 2006.
4. Silver FH and Landis WJ. Viscoelasticity, energy storage and transmission and dissipation by extracellular matrices in in vertebrates. In: Fratzl, P. (ed.) Collagen, Structure and Mechanics, Springer, New York, 2008;133-154.
5. Silver FH and Christiansen DL. Biomaterials Science and Biocompatibility, Springer, New York 1999.
6. Hulmes DJS. Collagen diversity, synthesis and assembly. In: Fratzl P (ed.) Collagen, Structure and Mechanics, Springer, New York 2008;15-47.
7. McBride DJ, et al. Morphological characterization of tendon development during chick embryogenesis: Measurement of birefringence retardation. Int J Biol Macromol 1985;7:71-76.
8. McBride DJ, et al. Structural and mechanical assessment of developing chick tendon. Int J Biol Macromol 1988;10:194-200.
9. Smith JW. Molecular pattern in native collagen. Nature 1968: 219: 157-158.

e-ISSN: 2321-6212
p-ISSN: 2347-2278

10. Doyle BB, et al. A D-periodic narrow filament in collagen. Proc R Soc Lond B 1974;186:67-74.

11. Pease DC and Bouteille M. The tridimensional ultrastructure of native collagen fibrils, cytochemical evidence for a carbohydrate matrix. J Ultrastur Res 1972;35:339-358.

12. Birk DE, et al. Matrix Polymerization. In: Hay ED (ed.) The Cell Biology of the Extracellular Matrix, Academic Press, N.Y., (2nd edn), 1991;221-254.

13. Silver FH, et al. Collagen self-assembly and development of matrix mechanical properties. J Biomechanics 2003;36:1529-1553.

14. Silver FH, et al. Type I Collagen Fibrillogenesis: Initiation Via Reversible Linear and Lateral Growth Steps. Biopolymers 1979;18:2523-2535.

15. Diamant J, et al. Collagen: ultrastructure and its relation to mechanical properties as a function of ageing, Proc Roy Soc Lond B 1872;180:293-315.

16. Torp S, et al. Effects of Age and of mechanical deformation on the ultrstructure of tendon. Proc Colston Conf, University of Bristol, UK 1974;26:223-250.

17. Parry DA, et al. A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and a possible relation between fibril size distribution and mechanical properties. Proc R Soc Lond B Biol Sci 1978;203:293-303.

18. Silver FH, et al. Analysis of mammalian connective tissue: Relationship between hierarchical structures and mechanical properties. J Long-Term Effects of Medical Implants 1992;2:165-172.

19. Horvath I, et al. Energy Analysis of Flow Induced Harmonic Motion in Blood Vessel Walls. Cardiovascular Eng 2005;5:21-28.

20. Shah R, et al. Morphomechanics of dermis-A method for non-destructive testing of collagenous tissues. Skin Res Tech 2016.

21. Shah R, et al. A method for non-destructive mechanical testing of tissues and implants. J Biomed Mat Res Part A 2017;105:5-22.

22. Sasaki N, et al. Time-resolved X-ray diffraction from tendon collagen during creep using synchrotron radiation. J Biomech 1999;32:285-292.

23. Folkhard W, et al. Structural dynamic of native tendon collagen. J Mol Biol 1987;193:405-407.

24. Freeman JW and Silver FH. Elastic energy storage in unimineralized and mineralized extracellular matrices (ECMs): A comparison between molecular modeling and experimental measurements. J Theor Biol 2004;229:371-381.

25. Paterlini MG, et al. The energy of formation of internal loops in triple-helical collagen polypeptides, Biopolymers 1995;35:607-619.