

AL-Mustaqbal University College
Department of Medical Physics
Biomaterials



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قسم الفيزياء الطبية
المواد الاحيائية
المرحلة الرابعة

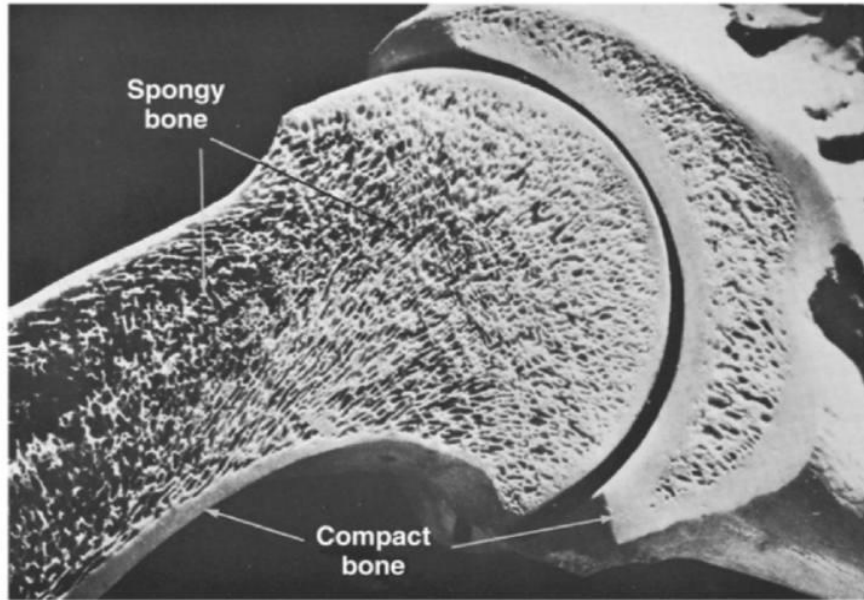
BIOMATERIALS

المحاضرة السابعة

STRUCTURE-PROPERTY RELATIONSHIPS OF BIOLOGICAL MATERIALS

م. م. نور الهدى صالح السلامي

STRUCTURE-PROPERTY RELATIONSHIPS OF BIOLOGICAL MATERIALS



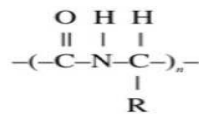
Sagittal section of the proximal end of the humerus in relation to the glenoid fossa of the scapula at the shoulder joint. These are dry bones, and the cartilaginous articular surfaces of the joint are not present.

The major difference between biological materials and biomaterials (implants) is viability. There are other equally important differences that distinguish living materials from artificial replacements. First, most biological materials are continuously bathed with body fluids. Exceptions are the specialized surface layers of skin, hair, nails, hooves, and the enamel of teeth. Second, most biological materials can be considered as composites. Structurally, biological tissues consist of a vast network of intertwining fibers with polysaccharide ground substances immersed in a pool of ionic fluid. Attached to the fibers are cells that comprise the living tissues. Physically, ground substances function as a glue, lubricant, and shock absorber in various tissues. The structure and properties of a given biological material are dependent upon the chemical and physical nature of the components present and their relative amounts. For example, neural tissues consist almost entirely of cells, while bone is composed of organic materials and

calcium phosphate minerals with minute quantities of cells and ground substances as a glue. An understanding of the exact role played by a tissue and its interrelationship with the function of the entire living organism are essential if biomaterials are to be used intelligently. Thus, a person who wants to design an artificial blood vessel prosthesis has to understand not only the property–structure relationship of the blood vessel wall but also its systemic function. This is because the natural artery is not only a blood conduit, but a component of a larger system, including a pump (heart), an oxygenator (lung), as well as neural systems that control stress in its walls, and a complex feedback system that governs cellular remodeling of the vessel structure.

7.1. PROTEINS

Proteins are polyamides formed by step-reaction polymerization between amino and carboxyl groups of amino acids:



where R is a side group. Depending on the side group, the molecular structure changes drastically. The simplest side group is hydrogen (H), which will form glycine (Gly). The geometry of the glycine is shown in Figure 7-1a, where the hypothetical flat sheet structure is shown. The structure has a repeating distance of 0.72 nm, and the side groups (R) are crowded, except for polyglycine, which has the smallest atom for the side group, H. If the side groups are larger, then the resulting structure is an D-helix, where the hydrogen bonds occur between different parts of the same chain and hold the helix together, as shown in Figure 7-1b.

9.1.1. Collagen

Collagen is a structural protein found in bone, cartilage, tendon, ligament, skin, and in the structural fibers of various organs. One of the basic constituents of protein is collagen, which has the general amino acid sequence–X–Gly–Pro–Hypro–Gly–X– (X can be any other amino acid) arranged in a triple D-helix. It has a high proportion of proline (Pro) and hydroxyproline (Hypro), as given in Table 7-1. Since the presence of hydroxyproline is unique in collagen (elastin contains a minute amount), the determination of collagen content in a given tissue is readily made by assaying the hydroxyproline.

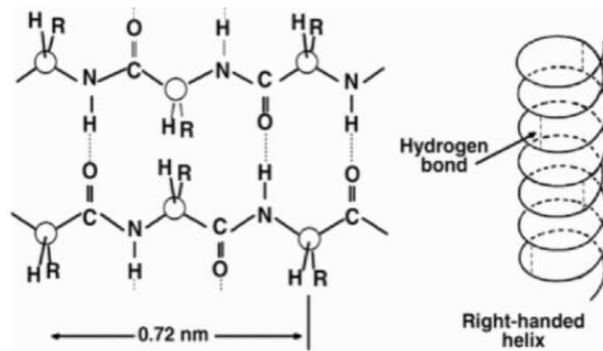


Figure 7-1. (a) Hypothetical flat sheet structure of a protein. (b) Helical arrangement of a protein chain.

Table 9-1. Amino Acid Content of Collagen

A.A. and component	Content (mol/100 mol amino acids)
Gly	31.4–33.8
Pro	11.7–13.8
Hypro	9.4–10.2
Acid polar a.a.s. (aspt. glut. asparagine)	11.5–12.5
Basic polar a.a.s. (lys. agr. his.)	8.5–8.9
Other a.a.s.	Residue

Three left-handed-helical peptide chains are coiled together to give a right-handed coiled superhelix with periodicity of 2.86 nm. This triple super helix is the molecular basis of tropocollagen, the precursor of collagen (see Figure 7-2). The three chains are held strongly to each other by H bonds between glycine residues and between hydroxyl (OH) groups of hydroxyproline. In addition, there are crosslinks via lysine among the (three) helices. The primary factors stabilizing the collagen molecules are invariably related to the interactions among the D-helices. These factors are H bonding between the C=O and NH groups, ionic bonding between the side groups of polar amino acids, and the interchain crosslinks between helices. The collagen fibrils (20–40 nm in diameter) form fiber bundles with a 0.2–1.2 Pm diameter. Figure 7-3 shows scanning and transmission electron microscopic pictures of collagen fibrils in bone, tendon, and skin. Note the straightness of tendon collagen fibrils compared to the more wavy skin fibers. The side groups of some amino acids are highly non-polar in character and hence hydrophobic; therefore, chains with these amino acids avoid contact with water molecules and seek the

greatest number of contacts with the non-polar chains of amino acids. If we destroy the hydrophobic nature by an organic solvent solution (e.g., urea), the characteristic structure is lost, resulting in microscopic changes such as shrinkage of collagen fibers. The same effect can be achieved by simply warming the collagen fibers. Another factor affecting the stability of the collagen is the incorporation of water molecules into the intra- and inter-chain structure. If the water content is lowered, the structural stability decreases. If the collagen is dehydrated completely (lyophilized), then the solubility also decreases (so-called in vitro aging of collagen).

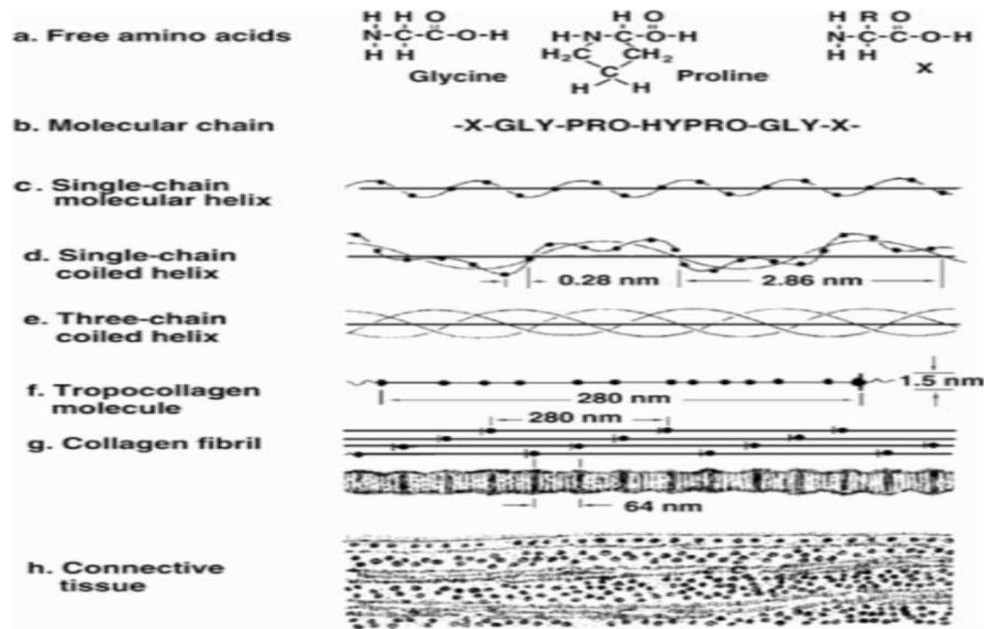


Figure 7-2. Diagram depicting the formation of collagen, which can be visualized as taking place in seven steps. The starting materials (a) are amino acids, of which two are shown, and the side chain of any others is indicated by R in amino acid X. (b) The amino acids are linked together to form a molecular chain. (c) This then coils into a left-handed helix (d and e). Three such chains then intertwine in a triple stranded helix, which constitutes the tropocollagen molecule (f). Many tropocollagen molecules become aligned in staggered fashion, overlapping by a quarter of their length to form a cross-striated collagen fibril (g).

It is known that the acid mucopolysaccharides also affect the stability of collagen fibers by mutual interactions by forming mucopolysaccharide-protein complexes. It is believed that the water molecules affect the polar region of the chains, making the dried collagen more disoriented than it is in the wet state.

7.1.2. Elastin

Elastin is another structural protein found in a relatively large amount in elastic tissues such as ligamentum nuchae (major supporting tissue in the head and neck of grazing animals), aortic wall, skin, etc. The chemical composition of elastin is somewhat different from that of collagen.

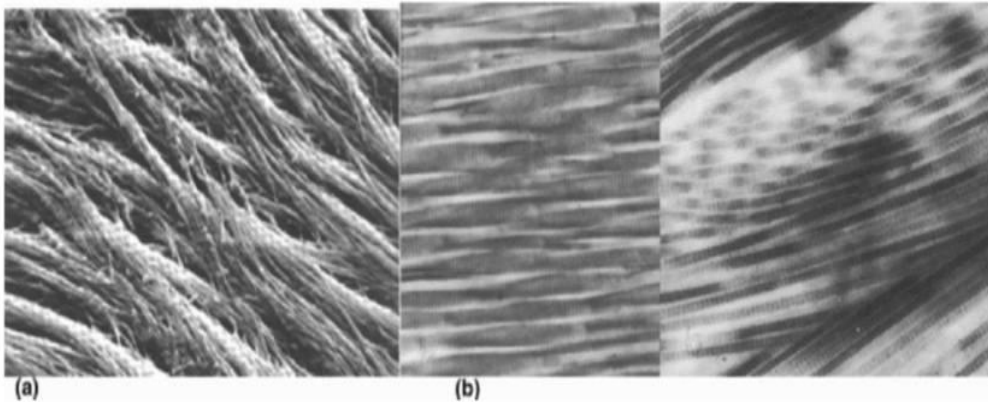


Figure 7-3. (a) Scanning electron micrograph of the surface of adult rabbit bone matrix, showing how the collagen fibrils branch and interconnect in an intricate.

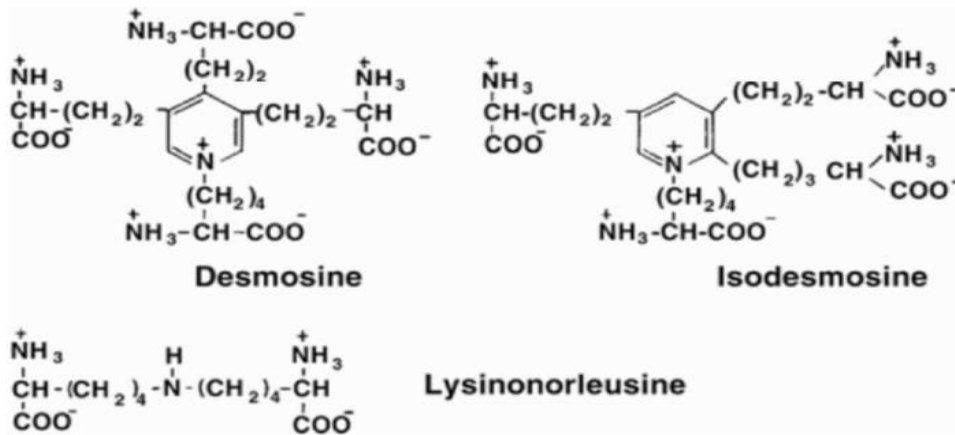


Figure 7-4. Structure of desmosine, isodesmosine, and lysinonorleucine.

The high elastic compliance and extensibility of elastin is due to the crosslinking of lysine residues via desmosine, isodesmosine, and lysinonorleucine (shown in Figure 7-4). The formation of desmosine and isodesmosine is only possible by the presence of copper and lysyl oxidase enzyme; hence, deficiency of copper in the diet may result in non-crosslinked elastin. This, in turn, will result in tissue that is viscous rather than normal rubber-like elastic tissue, and abnormality

that can lead to rupture of the aortic walls. Elastin is very stable at high temperature in the presence of various chemicals due to the very low content of polar side groups (hydroxyl and ionizable groups). The specific staining of elastin in tissue (prepared for microscopic study), by lipophilic stains such as Weigert's resorcin–fuchsin is due to the same reason. Elastin contains a high percentage of amino acids with aliphatic side chains such as valine (6 times that of collagen). It also lacks all the basic and acidic amino acids, so that it has very few ionizable groups. The most abundant of these, glutamic acid, occurs only a sixth as often as in collagen. Aspartic acid, lysine, and histidine are all below 2 residues per 1,000 in mature elastin. The composition of elastin is given in Table 7-2.

Table 7-2. Amino Acid Content of Elastin

Content	Amount (residues/1000)
Gly	324
Hypro	26
Cationic residues (Asp, Glu)	21
Anionic residues (His, Lys, Arg)	13
Nonpolar residues (Pro, Ala, Val, Met, Leu, Ile, Phe, Tyr)	595
Half-cystine	4

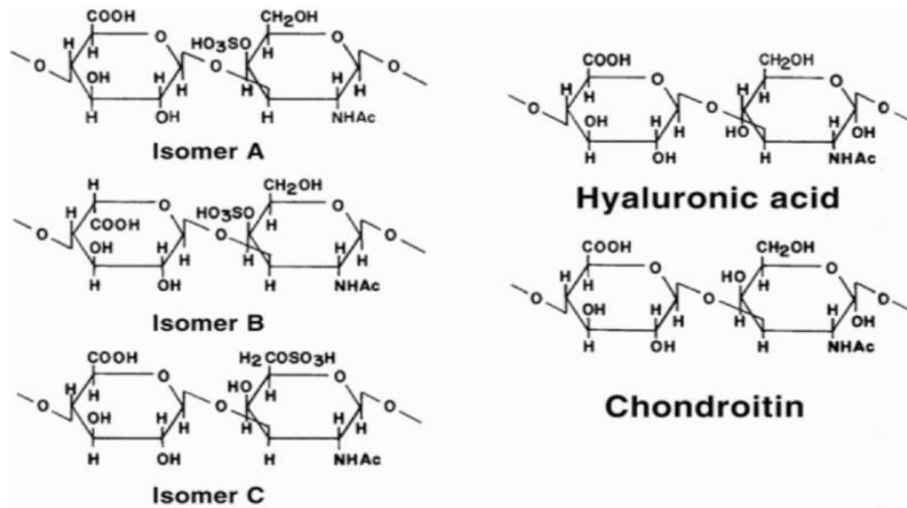


Figure 7-5. Structure of hyaluronic acid, chondroitin, and chondroitin sulfates.

9.2. POLYSACCHARIDES

Polysaccharides are polymers of simple sugars. They exist in tissues as a highly viscous material that interacts readily with proteins, including collagen, resulting in glycosamino–glycans (also known as mucopolysaccharides) or proteoglycans. These molecules readily bind both water and cations due to the large content of anionic side chains. They also exist at physiological concentrations not as viscous solids but as viscoelastic gels. All of these polysaccharides consist of disaccharide units polymerized into unbranched macromolecules, as shown in Figure 7-5.

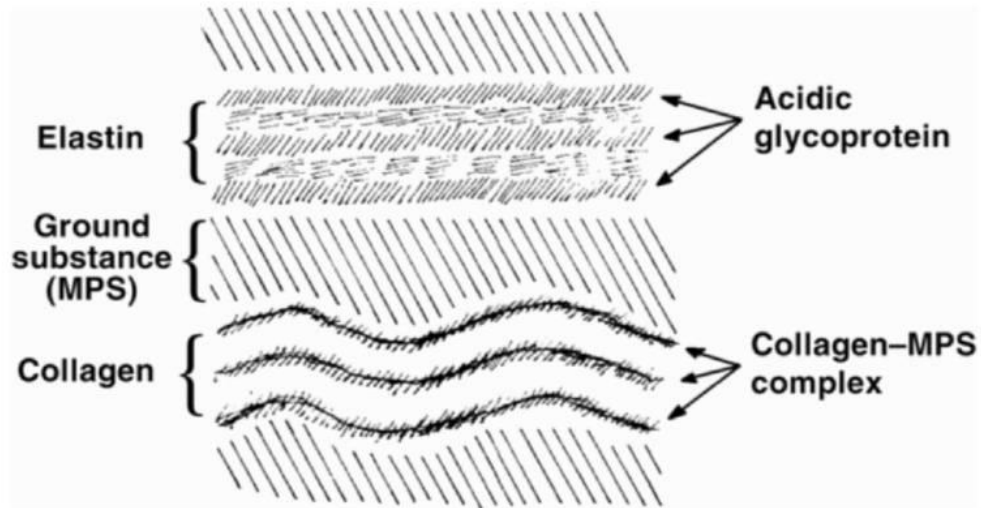


Figure 7-6. Schematic representation of mucopolysaccharides—protein molecules in connective tissues. Note the wavy nature of collagen fibers and the straighter form of elastin.

9.2.1. Hyaluronic Acid and Chondroitin

Hyaluronic acid is found in the vitreous humor of the eye, synovial fluid, skin, umbilical cord, and aortic walls. Hyaluronic acid is made of residues of N-acetylglucosamine and Dglucuronic acid, but it lacks the sulfate residues. The animal hyaluronic acid contains a protein component (0.33 w/o or more) and is believed to be chemically bound to at least one protein or peptide that cannot be removed. This, in turn, will result in proteoglycan molecules that may behave differently from the pure polysaccharides. Chondroitin is similar to hyaluronic acid in its structure and properties and is found in the cornea of the eyes.

9.2.2. Chondroitin Sulfate

This is the sulfated mucopolysaccharide that resists the hyaluronidase enzyme. It has three isomers, as shown in Figure 7-5. Isomer A (chondroitin 4-sulfate) is found in cartilage, bones, and the cornea, while isomer C (chondroitin 6-sulfate) can be isolated from cartilage, umbilical cord, and tendon. Isomer B (dermatan sulfate) is found in skin and the lungs and is resistant to testicular hyaluronidase enzyme. The chondroitin sulfate chains in connective tissues are bound covalently to a polypeptide backbone through their reducing ends. Figure 7-6 shows a proposed macromolecular structure of protein-polysaccharides from which one can imagine the nature of the viscoelastic properties of the ground substance. These complexes of protein and mucopolysaccharides (ground substance) play an important role in the physical behavior of connective tissues either as lubricating agents between tissues (e.g., joints) or between elastin and collagen microfibrils.

Example 1

Calculate the degree of polymerization of a chondroitin compound that has an average molecular weight of 100,000 g/mole.

Answer//

From Figure 7-5 (also Ac is COOCH_3 , acetyl) it can be seen that there are 14 carbon atoms, 13 oxygen atoms, 21 hydrogen atoms, and 1 nitrogen atom in a repeating unit; therefore, $12 \times 14 + 14 \times 16 + 21 \times 1 + 1 \times 14 = 427$, and

$$\text{D.P.} = 100,000/427 = 234$$

9.3. STRUCTURE-PROPERTY RELATIONSHIP OF TISSUES

Understanding the structure-property relationship of various tissues is important since one has to know what is being replaced by the artificial materials (biomaterials). Also, one may want to use natural tissues as biomaterials (for example, porcine heart valves). The property measurements of any tissues are confronted with many of the following limitations and variations:

1. Limited sample size,
2. Original structure can undergo change during sample collection or preparation,
3. Inhomogeneity,
4. Complex nature of the tissues makes it difficult to obtain fundamental physical parameters,
5. Tissue cannot be frozen or homogenized without altering its structure or properties.
6. The in-vitro and in-vivo property measurements are sometimes difficult, if not impossible, to correlate.

The main objective of studying the property–structure relation of tissues is to design better performing implants in our body. Therefore, one should always ask, “What kind of physiological functions are being performed by the tissues or organs under study in vivo and how can one best assume their lost function?” Keeping this in mind, let us study the tissue structure– property relationships.

Words

Aspartic acid (Asp): One of the essential amino acids.

Canaliculi: Small channels (~0.3 Pm in diameter) radiating from the lacunae in bone tissue.

Cementum: Calcified tissue of mesodermal origin covering the root of a tooth.

Chondroitin: One of the polysaccharides commonly found in the cornea of the eye.

Chondroitin sulfate: Sulfated mucopolysaccharides commonly found in cartilages, bones, cornea, tendon, lung, and skin.

Desmosine: One of the crosslinking chemicals in elastin.

Elastin: One of the proteins in connective tissue. It is highly stable at high temperatures and in chemicals. It also has rubber-like properties; hence it is nicknamed “tissue rubber”

Glutamic acid (Glu): One of the essential amino acids, much more commonly occurring in collagen than in elastin.

Glycine (Gly): One of the amino acids having the simplest structure.

Haversian system: Same as “osteon.”

Histidine (His): One of the amino acids.

Hyaluronic acid: One of the polysaccharides commonly found in synovial fluid, aortic walls, etc.

Hydroxyapatite: Mineral component of bone and teeth. It is a type of calcium phosphate, with composition $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$

Hydroxyproline (Hypro): One of the amino acids commonly occurring in collagen molecules.