Chapter 1
Collagen: Structure and Mechanics, an Introduction

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Abstract Collagen type I is the most abundant protein in mammals. It confers mechanical stability, strength and toughness to a range of tissues from tendons and ligaments, to skin, cornea, bone and dentin. These tissues have quite different mechanical requirements, some need to be elastic or to store mechanical energy and others need to be stiff and tough. This shows the versatility of collagen as a building material. While in some cases (bone and dentin) the stiffness is increased by the inclusion of mineral, the mechanical properties are, in general, adapted by a modification of the hierarchical structure rather than by a different chemical composition. The basic building block of collagen-rich tissues is the collagen fibril, a fiber with 50 to a few hundred nanometer thickness. These fibrils are then assembled to a variety of more complex structures with very different mechanical properties. As a general introduction to the book, the hierarchical structure and the mechanical properties of some collagen-rich tissues are briefly discussed. In addition, this chapter gives elementary definitions of some basic mechanical quantities needed throughout the book, such as stress, strain, stiffness, strength and toughness.

1.1 Collagen-Based Tissues

Collagen is among the most abundant fibrous proteins and fulfills a variety of mechanical functions, particularly in mammals. It constitutes the major part of tendons and ligaments, most of the organic matrix in bone and dentin; it is present in skin, arteries, cartilage and in most of the extracellular matrix in general. Collagen is also used by invertebrates, for example in the byssus threads, by which mussels are attached to rocks (Waite et al. 2003).

More generally, fibrous polymers are the major building blocks in all types of load-bearing tissues from unicellular organisms in water to plants and animals (Jeronimidis 2000). These fibers include polysaccharides, such as cellulose and chitin, extremely abundant in plants and in insect cuticles, respectively, and a variety of proteins. In addition to collagen, structural proteins include keratin, predominant in hair and nails, silk as used by spiders, for example, and actin, present in muscle and the cytoskeleton of every cell. Many more fibrous proteins with more

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specialized functions are used by different organisms. A general introduction to this theme can be found in Elices (2000) and Shewry et al. (2003).

From a mechanical viewpoint, fibrous tissues are very special (Vincent 1990, Jeronimidis 2000). Such materials are usually much stronger in fiber direction than perpendicular to it. As a consequence, properties are anisotropic, which can be reduced by special construction principles, such as plywood assemblies to form laminates (Weiner and Wagner 1998). In fact, a large variety of overall properties can easily be achieved by a clever assembly of fibers. We know from our daily life experience how, based on fibers, it is possible to make strong ropes for uniaxial loading or tissues with high or low elasticity, depending on the weaving. In a very similar way, tissues and whole organs are constructed with fibers by hierarchical assembly leading to a large variety of mechanical properties (Fratzl 2003). Understanding the hierarchical structure of biological materials is, therefore, a key to the understanding of their mechanical properties (Tirrell 1994, Fratzl and Weinkamer 2007). Collagen is no exception to this and we find it in very complex hierarchical structures with quite different properties, such as elastic skin, soft cartilage, and stiff bone and tendon.

Hierarchical structuring has the advantage to allow for optimization and mechanical adaptation at every structural level (Fratzl and Weinkamer 2007). For most biological materials (Wainwright 1982), including plants (Niklas 1992, Mattheck 1998), the internal architecture determines the mechanical behavior more than the chemical composition does. To illustrate this fact, let us take two extremely simple examples. The first is a composite of stiff fibers in a soft matrix and the second is a honeycomb structure. Using the Voigt and the Reuss model for a fiber composite as sketched in Fig. 1.1a (Hull and Clyne 1996), where the volume fraction of the matrix phase is called Φ, the elastic young modulus in axial and lateral directions are given as a function of the moduli E_m and E_f of matrix and fibers, respectively, by

$$E_\mathrm{A} = \Phi\, E_\mathrm{m} + (1-\Phi)\, E_\mathrm{f}, \text{ and } E_\mathrm{L} = \left(\Phi\, E_\mathrm{m}^{-1} + (1-\Phi)\, E_\mathrm{f}^{-1}\right)^{-1} \tag{1.1}$$

If the Young's moduli (for a definition see below) of matrix and fiber are very different, these two expressions predict an extremely different mechanical behavior of the

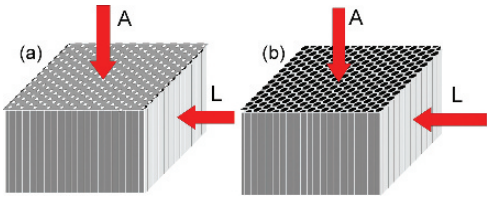

Fig. 1.1 Model for a fiber-reinforced composite (**a**) and a honeycomb structure (**b**). The matrix phase is shown in grey. The fibers in (**a**) are indicated by white circles and the holes in the honeycomb (**b**) by black hexagons. The A and L directions correspond to loading in axial and lateral directions, respectively

composite loaded in axial and lateral directions. Similarly, considering a honeycomb structure as sketched in Fig. 1.1b, the elastic moduli in axial and lateral directions, respectively, can be estimated to be (Gibson and Ashby 1999)

$$E_A/E_m \propto \Phi, \text{ and } E_L/E_m \propto \Phi^3 \tag{1.2}$$

Again, with thin walls in the honeycomb structure (that is, $\Phi << 1$), the difference between lateral and axial mechanical properties can be orders of magnitude. These two examples show that by simple structuring, mechanical properties can vary enormously, even though the chemical composition is the same. In particular, the local fiber orientation plays a major role for adapting the mechanical properties of most biological materials.

Taking the example of bone (Cowin 2001, Currey 2002), structural optimization means that every bone in our body will – according to its mechanical function – have a slightly different arrangement of the basic building blocks, the mineralized collagen fibrils. The consequence is that bending stiffness, fracture resistance and other mechanical properties will differ from site to site as a consequence of the different local architecture. Hence, it is very difficult to talk about the (mechanical) properties of a tissue, such as bone or tendon, in a general way, since these properties depend on local architecture and on the actual mechanical needs dictated by the environment in the living body. This is the reason why (hierarchical) structure and mechanical properties are addressed in this book simultaneously. Indeed, they cannot be considered separately.

This book focuses on mammalian collagen type I which is the major organic constituent of tendon, bone and dentin, and plays a crucial role in blood vessels, skin and extracellular matrix, in general. The first part (Chapters 2–4) concentrates on general aspects with reviews of the various collagen types and assemblies (Chapter 2), the structure of the collagen fibril, the basic building block of all tissues based on collagen I (Chapter 3), and the chemistry and biology of cross-links between collagen molecules, which are of particular importance for the mechanical behavior (Chapter 4). General aspects of the mechanical behavior of collagen-based tissues are reviewed in the second part of this book. This includes damage and fatigue (Chapter 5), viscoelasticity and energy storage in extracellular matrices, including tendon, skin and cartilage (Chapter 6), and nanoscale deformation mechanisms, both from an experimental (Chapter 7) and from a theoretical materials mechanics viewpoint (Chapter 8). This is complemented by a review of the biological repair mechanisms in extracellular matrix tissues (Chapter 9). A number of special collagen-rich tissues are finally addressed in the third part of this book, including tendon and ligament (Chapter 10), artery walls (Chapter 11), the extracellular matrix of skeletal and cardiac muscle (Chapter 12), cornea and sclera (Chapter 13), bone and calcified cartilage (Chapter 14) and dentin (Chapter 15). The last two chapters address genetic collagen diseases (Chapter 16) and biomimetic collagen tissues, particularly in the context of tissue engineering (Chapter 17).

This book considers a wide selection of collagen-rich tissues in mammals but avoids a particular focus on those tissues, which have been most widely studied in

the context of structure and mechanical properties because of their medical importance, namely bone (see. e.g., Cowin 2001, Currey 2002, Weiner and Wagner 1998, Fratzl et al. 2004) and cartilage (see, e.g., Bader and Lee 2000), as there are several relevant text books and review articles.

Chapter 1 introduces some basic mechanical parameters in an elementary way, which will be needed throughout this book. It also gives general comments on the hierarchical structure and the mechanical properties of collagen-rich tissues, pointing out where more details can be found in this book.

1.2 Basic Mechanical Parameters

1.2.1 Stress and Strain

When an elementary volume is subjected to tensile forces, for example, the material will typically elongate in the direction of the applied forces. The relative elongation is called strain, often denoted ε (see Fig. 1.2). Usually, this elongation leads to a contraction of the material in the direction perpendicular to the applied stress, by a relative amount $\nu\varepsilon$, where the coefficient ν is called Poisson ratio. For an isotropic piece of material, the relative increase of the volume during uniaxial stretching is $1–2\nu$ which means that the Poisson ratio has an upper bound of $\nu \leq 1/2$, because the specimen volume is not expected to shrink under the influence of tensile forces. A typical value for the Poisson ratio is $\nu = 1/3$. The load (force in N) divided by the surface area A ($A = L^2$, for the sketch in Fig. 1.1) is called stress (units Pascal).

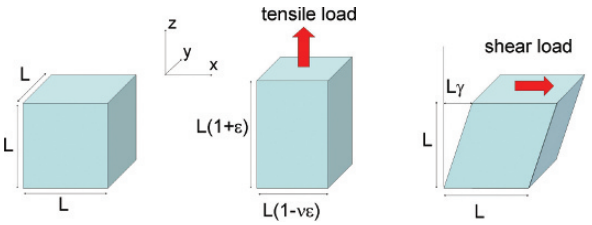

Fig. 1.2 When a cubic piece of material is subjected to tensile load along the vertical (z-direction) only, its length L is increased by $L\varepsilon$. The relative elongation ε is called (tensile) strain. In most cases, the dimensions of the cube subjected to tensile load will contract perpendicularly to the load direction. The ratio ν of the contraction in the x-direction (or in the y-direction) relative to the elongation in z-direction is called the Poisson ratio. When the load is tangential to the top surface, (*right picture*), shear deformation occurs. The shear is measured by the parameter γ, which (for small deformations) corresponds to the tilting angle of the cube edge initially parallel to the z-direction

Generally, stresses and strains are not just uniaxial and need to be described by a tensor. More general definitions can be found in text books on mechanics of materials, see for example, Hull and Clyne (1996).

1.2.2 Elastic and Viscoelastic Behavior

A first inspection of the mechanical behavior of materials is possible by measuring the relation between stress σ and strain ε. Figure 1.3 shows some examples for different types of mechanical behavior, when the material is subjected to a tensile stress σ. Typically the stress increases first linearly, when the strain increases. The ratio between stress and strain (that is, the slope of the σ–ε curve at small ε, see Fig. 1.3) is called Young's modulus E, and $\sigma = E\,\varepsilon$. For larger strains, this linearity is not necessarily conserved. When the same σ–ε curve is followed during a release of the stress and during build up, the mechanical behavior is called elastic. A linear elastic material is the special case where the σ–ε curve is linear. In many cases, materials show a linear elastic behavior at small deformations, but do not return to their original shape when the stress has exceeded a critical value (often called yield stress). Such a material behavior is called plastic and the permanent elongation is the associated plastic deformation. Bone, for example, shows some plastic behavior (see Chapter 14 and Fig. 14.6).

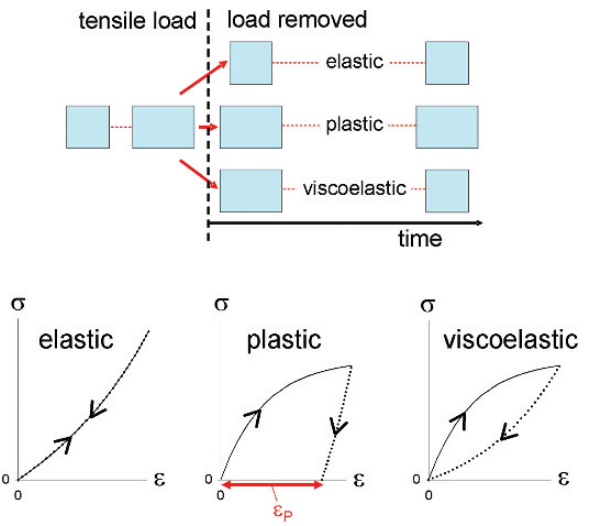

Fig. 1.3 Materials behave differently when the load is removed after deformation (*left*). An elastic material returns immediately to its original shape, a plastic material keeps the deformed shape forever and a viscoelastic material returns slowly to its original shape. Materials often have a combination of those properties: An elastoplastic material relaxes partially and retains only part of the deformation. Similarly, a viscoplastic material loses gradually a part of the deformation but a fraction of it stays forever. In a stress–strain experiment (*right*), the stress σ is measured as a function of strain ε. Full lines in the σ–ε curves show increasing stress and dotted lines decreasing stress. For elastic materials, these two lines coincide. If this line is non-linear (as occurs for many polymeric materials), the elasticity is called non-linear. Close to the origin (near zero stress), nearly all materials are linearly elastic. For plastic materials, a permanent strain ε_P remains after sufficiently large deformation. For viscoelastic materials, there is a hysteresis. The elastic modulus E is defined as the slope of the full line close to the origin

Many biological tissues, including collagen, are viscoelastic. One possible reason is that a viscous fluid (often just water) is flowing during deformation. The simplest model for such behavior is the so-called Kelvin model, where a dashpot (providing fluid friction) is supposed to act in parallel to an elastic spring. The equation of deformation then depends both on the strain ε and its time derivative $\dot{\varepsilon}$, and reads (Puxkandl et al. 2002)

$$\sigma = E\,\varepsilon + \eta\,\dot{\varepsilon} \tag{1.3}$$

As a consequence, the mechanical behavior becomes time dependent. This is illustrated by a simple example below. A more complete discussion of viscoelastic behavior in biological materials can be found, e.g., in (Vincent 1990).

Now we consider the simple example where the externally applied stress σ is first increased to σ_0 at constant speed during time t_0 and then decreased at the same speed (see Fig. 1.4). To solve Eq. (1.3) in this case, we rewrite it in non-dimensional units

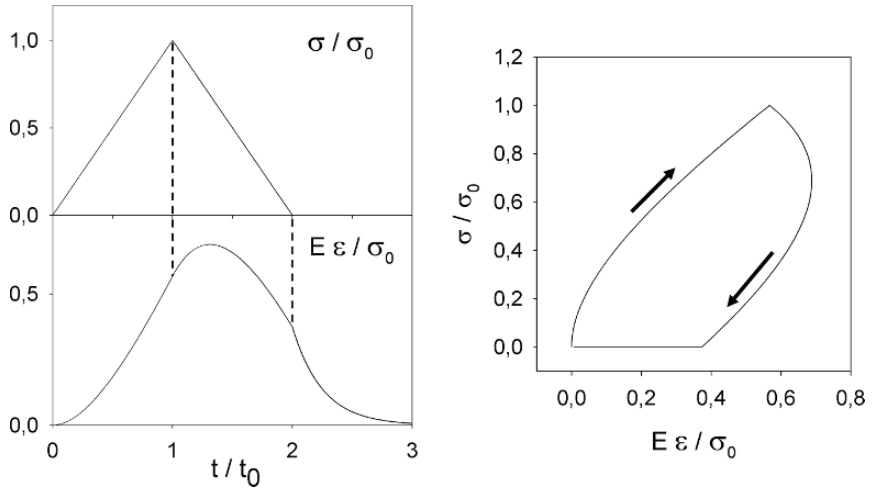

Fig. 1.4 Solution of Eq. (1.4) for $\lambda = 1/2$ and an imposed time variation of the stress as shown on the top left. The applied stress first increases and then decreases linearly, before staying completely at zero. Due to the viscoelastic behavior of the material, the strain is not increasing as fast as the stress, since some of the stress is needed to compensate the forces generated by viscosity rather than by strain in the material. Note that the strain continues to increase even after the stress has reached its peak value (*left broken line*), as a consequence of the relaxation of the frictional forces inside the material. Only after the stress has dropped further, the strain decreases but does not reach zero when all the stress is removed (*second broken line*). It then takes a while before all the strains are removed in a creep process. The consequence for the stress–strain curve (*right*) is that the curves corresponding to increasing and to decreasing stress do not overlap. The area between the two curves corresponds to the energy per unit volume dissipated by viscous friction during the mechanical cycle

$$y = x + \lambda \frac{\mathrm{d}x}{\mathrm{d}\tau}, \quad \text{where} \quad \begin{cases} y = \sigma/\sigma_0 \\ x = E\,\varepsilon/\sigma_0 \\ \tau = t/t_0 \\ \lambda = \eta/(E\,t_0) \end{cases} \tag{1.4}$$

Fig. 1.4 shows the solution of this equation for $\lambda = 1/2$ and an imposed time variation of the stress. The stress–strain curve becomes fairly complex and dependent on the strain rate. In particular, the σ–ε curves are not the same during increase and decrease of the applied stress. Moreover, energy is being dissipated by viscous friction in the material. This may be important for damping or dissipating the energy in an impact (see Chapter 5). It may also cause energy loss in a cyclic movement (see Chapter 6).

1.2.3 Stiffness, Strength and Toughness

Young's modulus E, introduced in the previous section, describes the stiffness of a material, that is, its resistance against deformation when subjected to a given stress. Stiff materials are needed to transmit forces (for example, in tendons and ligaments) and to resist deformation. Stiffness is especially crucial for transmitting forces when the material is loaded in bending. This may be one of the reasons why bones are reinforced with extremely stiff mineral particles. Stiffness is also needed for resistance against buckling when a bar is loaded in compression along its axis.

But stiffness is by no means the only critical mechanical property (see Fig. 1.5). The strength of a material is defined as the maximum stress it can sustain before breaking. The strength is often denoted by σ_f. High strength is needed to allow

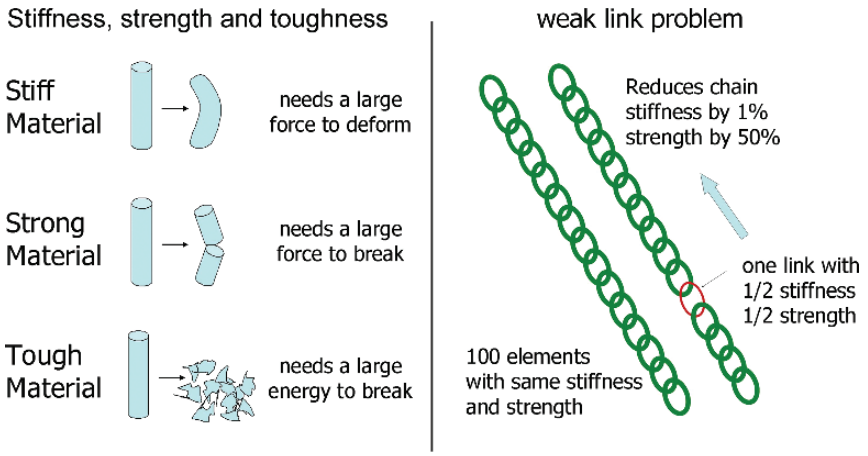

Fig. 1.5 Some mechanical characteristics of a material, and the weak link problem in a chain

carrying high loads. Tendons, ligaments or bones need to be strong. Technical materials used for construction are usually both stiff and strong. There is, however, a subtle but essential difference in how these properties are affected by defects in a homogeneous material. This may be understood by the "weak link" problem (Fig. 1.5). A simple calculation shows that if one of 100 identical elements in a chain is replaced by a link with half the stiffness and half the strength, the overall stiffness of the chain is reduced just by 1% but the overall strength is only half. This means that the stiffness (as a bulk property) is hardly influenced by small defects while the strength depends heavily on local properties and on defects. As a consequence, the strength of ceramics is almost completely controlled by the size and the amount of defects in the material, to an extent, where the strength becomes a statistical property of the ceramic (depending on the defect distribution) rather than an intrinsic one (Lawn 1993).

This dependence on defects and material inhomogeneities is even worse for yet another crucial material property, the toughness (see Fig. 1.5). The toughness is linked to the energy needed to propagate a crack through the material and to break it. The larger the energy needed, the tougher the material is. Brittle ceramics, for example, have a very low toughness, but they are typically very stiff. Indeed, a major way for a material to dissipate energy in an impact is to deform rather than to fracture. Therefore, many materials which deform easily are also tough, while very stiff materials (such as ceramics) have a higher chance to be brittle. This is a major dilemma in materials design, since both stiffness and toughness are needed for many applications. It is quite interesting to observe (see below) that collagen-based tissues, such as tendon or bone, represent an excellent compromise between stiffness, strength and toughness.

A first estimate for the toughness is given by the area under the stress–strain curve when the material is loaded until failure. This area corresponds to the energy per unit volume needed to break the material, measured in $\mathrm{J/m^3}$. A better definition is given in terms of the energy per unit of crack advance area, needed to elongate a pre-existing crack: This energy is often called work of fracture or energy release rate, G, and measured in $\mathrm{J/m^2}$. The quantity $K = \sqrt{E\,G}$ is usually referred to as fracture toughness (see, e.g., Hull and Clyne 1996). Since, Young's modulus, E, is given in Pa, the fracture toughness is measured in somewhat unusual units of $\mathrm{Pa}\sqrt{\mathrm{m}}$. The difference between these two estimates is that the fracture toughness describes the energy dissipation by an existing crack which moves, while the area under the stress–strain curve includes the initiation/nucleation of a macroscopic crack. Details of fracture mechanics in the context of collagen-rich tissues can be found in Chapter 5. Usually, the toughness of a material is determined by the ability of its microstructure to dissipate deformation energy without propagation of a critical crack. Polymers are often able to dissipate energy by viscoplastic flow or by the formation of non-connected microcracks, and collagen-rich tissues are no exception (see Chapters 5, 7, 14 for tendon and bone). Well-known toughening mechanisms in ceramics are crack ligament bridging and crack deflection. Most interestingly, all these phenomena are typically identified in tough collagen-rich tissues, such as bone (Peterlik et al. 2006).

1.3 Mechanical Properties of Collagen-Based Tissues

To illustrate some of the mechanical properties introduced above, Fig. 1.6 shows typical stress–strain curves for a tendon from the mouse tail (Misof et al. 1997) and for parallel-fibered bone obtained from a certain region in the cortex of bovine femur (Gupta et al. 2006). Both tissues have in common that they were loaded in tension in the direction of the collagen fibrils. While this is the usual loading case for tendons, both the loading and the structure can be much more complex in bone. Indeed, bone is often loaded in compression and in bending rather than just in tension. Moreover, the bone structure consists very rarely of parallel collagen fibrils. In most cases (see Fig. 1.8), the structure is much more complex with a plywood-like arrangement of fibrils (Weiner and Wagner 1998, Giraud-Guille 1988).

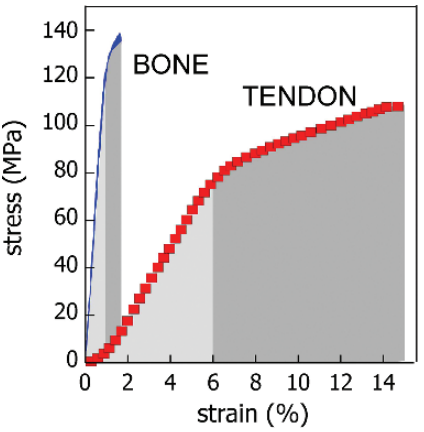

Fig. 1.6 Typical stress–strain curves for mouse tail tendon (Misof et al. 1997) and for parallel-fibered bone (Gupta et al. 2006). The area shaded in darker gray corresponds to the energy per unit volume dissipated in the post-yield deformation. The area shaded in lighter gray indicates the elastic energy per unit volume stored during deformation

The difference in the mechanical behavior between tendon and bone shown in Fig. 1.6 is, therefore, not due to different fiber architectures but due to the fact that bone is mineralized. The inclusion of tiny calcium-phosphate mineral particles leads to a considerable stiffening of the tissue, from roughly 1 GPa for tendon (Chapter 10) to about 20 GPa for bone (Chapter 14), as is visible by the change in the initial slope of the curve in Fig. 1.6. The price to pay for this higher stiffness is a smaller area under the stress–strain curve, which indicates a lower toughness of bone compared to tendon. Generally, the work of fracture decreases with the mineral content (Chapter 14). The light shaded area shows the elastic region of the stress–strain curve and corresponds to the elastic energy per unit volume which may be stored in the tissue during a loading cycle (see Chapter 6). Note that the stress–strain curve of tendon is not quite linear in the elastic region at small strains. The origin of this behavior and the deformation mechanisms of bone and tendon at the fibril and

sub-fibril levels are discussed in detail in Chapter 7. Due to the complex hierarchical structure of collagen, its description in terms of theoretical models has just started. The state of the art in the hierarchical modeling of collagen is reviewed in Chapter 8. Other types of models for skin and artery walls are discussed in Chapter 11.

The dark shaded areas in Fig. 1.6 highlight the regions of post-yield deformation where damage and plastic deformation occurs in the tissue. These processes are irreversible but contribute to the dissipation of mechanical energy and, therefore, to the toughness of these tissues. Damage, fracture and fatigue of collagen-rich tissues are reviewed in Chapter 5. Most interestingly, there is a biological response to mechanical stimuli which leads to the adaptation of biological tissues as well as to damage repair. This involves mechanosensitivity of the cells in the tissue and a process called remodeling, whereby damaged tissue is removed and replaced by new tissue, according to mechanical needs (Cowin 2001, Fratzl and Weinkamer 2007, for a discussion of remodeling in bone). Chapter 9 reviews tissue adaptation and remodeling in extracellular matrix and, in particular, tendon.

1.4 Hierarchical Structure of Collagen-Based Tissues

Collagen-rich tissues are typically based on the collagen fibril as an elementary building block. These fibrils have a thickness in the range from 50 to a few hundred nanometers and are assembled in a complex hierarchical way into macroscopic structures. The hierarchical structure of tendon is shown as an example in Fig. 1.7. Several levels of fiber-like structures can be seen in this figure. At the lowest level, there are the collagen molecules, which are triple-helical protein chains with a length of about 300 nm. Details on the synthesis and the assembly of such collagen type I molecules, as well as many others of the collagen family are given in Chapter 2. The collagen molecules are further assembled by a parallel staggering into fibrils. As indicated in Fig. 1.7, neighboring

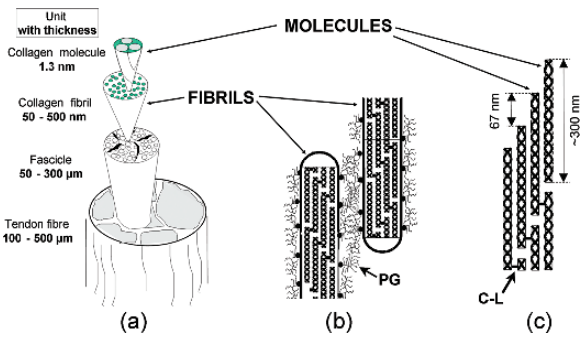

Fig. 1.7 Sketch of the hierarchical structure of tendon (adapted from Fratzl and Weinkamer 2007). (**a**) shows some of the units, fiber, fascicle, fibril and molecule. (**b**) and (**c**) show details of the interaction between fibrils and molecules, respectively. The proteoglycan-rich matrix between fibrils is indicated by PG and cross-links between collagen molecules by C-L

molecules are shifted by about 67 nm inside the fibrils. The three-dimensional structure of collagen fibrils are reviewed in detail in Chapter 3. One aspect, particularly important for the mechanical properties of fibrils, corresponds to covalent cross-linking between molecules which develops only with maturation of the tissues. All aspects related to cross-linking are reviewed in Chapter 4. Once collagen molecules have been synthesized, they assemble spontaneously outside the cell (see Chapters 2 and 3). This can be used for the biomimetic assembly of collagen tissues for tissue engineering and other applications (see Chapter 17).

Moreover, the fibrils are joined by a matrix rich in proteoglycans which also contributes significantly to the mechanical behavior of tendons (Chapter 7). There is a wide range of genetic diseases which affect collagen molecules and, as a consequence, their ability to assemble into the right type of hierarchical structures. The most notable example is osteogenesis imperfecta, the brittle bone disease. Such diseases and their consequences for structure and mechanical properties of collagen-based tissues are reviewed in Chapter 16.

The mechanical functions of tendons and ligaments are discussed in Chapter 10. While tendons and ligaments are mostly needed to transfer forces from the muscles to the bones and to store elastic energy for better locomotion (see Chapter 6), other collagen-rich organic tissues have to fulfill quite different functions. In the case of the cornea, for example, the tissue not only confers mechanical stability to the eye bulb, but also needs to be transparent, which puts certain structural constraints on the tissue. The knowledge in this field is reviewed in Chapter 13. Skin and artery walls need to be flexible but arteries also need to resist blood pressure. This implies yet a quite different arrangement of collagen fibrils in combination with elastomeric molecules, such as elastin, for example. Chapter 11 reviews the structure of artery walls and discusses biomechanical models of this tissue. Even muscles could not function without a scaffold rich in collagen in which the muscle cells are embedded. Chapter 12 reviews the structure and function of extracellular matrix in muscle tissue.

Finally, in bone and dentin, the organic matrix alone is not sufficient to provide the stiffness required for these tissues which have to carry considerable (compressive) loads. The stiffening is provided by the inclusion of mineral particles into the collagen-rich tissue. The mineral phase occupies about half the volume in compact bone. Figure 1.8 shows the example of cortical (compact) bone from a human femur. The basic building block is the mineralized collagen fibril (Fig. 1.8d,e) with a structure very similar to what is found in tendon (Fig. 1.7) but containing plate-shaped mineral particles with 2–4 nm thickness made of carbonated hydroxyapatite. These fibrils are then assembled in a plywood-like fashion to lamellar bone (Weiner and Wagner 1998). Figure 1.8c shows an example of lamellar bone surrounding a blood vessel. The unit comprising the central canal in an osteon and most of the compact bone in a human femur is formed by osteons (Fig. 1.8b). The mechanical properties of bone and dentin depend to a large extent on the degree of mineralization and on the fiber architecture. Chapters 14 and 15 discuss these relations for bone and for dentin, respectively.

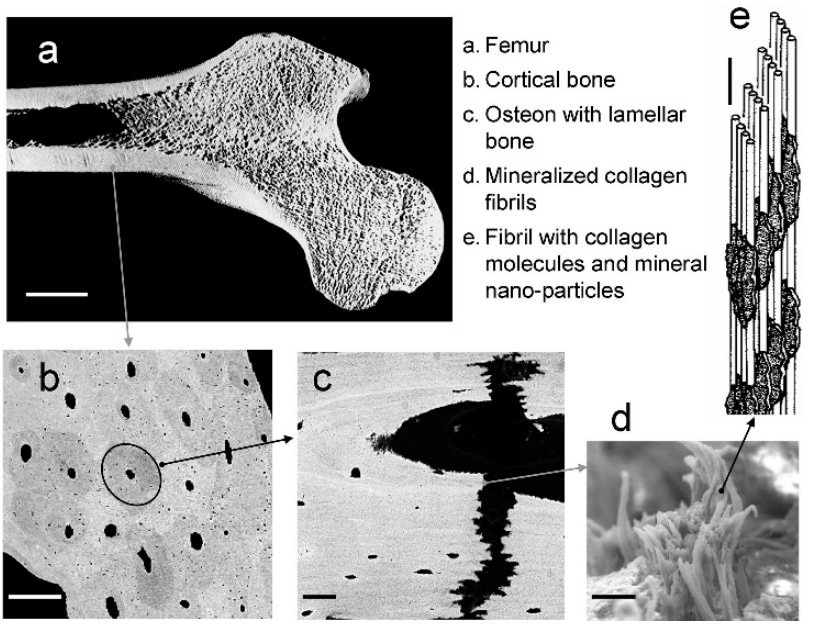

Fig. 1.8 Hierarchical structure of cortical bone (adapted from Fratzl et al. 2004 and from Peterlik et al. 2006). The length of the bar is 20 mm, 200 μm, 20 μm, 2 μm and 100 nm in (**a**)–(**e**), respectively. The ellipse in (**b**) indicates an osteon of the type shown in (**c**). In addition, (**c**) shows a crack propagating through lamellar bone in an osteon during a fracture experiment (Peterlik et al. 2006)

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