4
Aging and Degeneration of Tendons

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Introduction: Aging

The process of aging is a universal, decremental, and intrinsic process which should be considered innate to our genetic design—not pathological [1]. The rate of aging is highly individual and depends on many factors, including genetics, lifestyle, and former disease processes [2].

Overuse tendinopathies are common in primary care. These tendon problems are not restricted to competitive athletes but affect recreational sports participants and many working people. The pathology underlying these conditions is usually tendinosis or collagen degeneration [3]. Kannus and coworkers [4] showed in a 3-year prospective controlled study that sports injuries in elderly athletes are more frequently overuse-related than acute and commonly have a degenerative basis.

The degenerative changes associated with increasing age may be detected as early as the third decade, when a progressive decline becomes apparent in cellular function in many tissues [5]. With aging, various functions of the body gradually deteriorate. This also includes the musculoskeletal system, even if not so extensively as the cardiovascular system [6]. The tendon is subjected to early degenerative changes, since both the collagen and noncollagenous matrix components of tendons show qualitative and quantitative changes. There are also many cellular and vascular changes within the aging tendon. However, in adults, studies have not found a clear correlation between macroscopic tendon characteristics, such as thickness and surface area, and age [7,8].

As a result of all these physiological age-related changes, an aged tendon is weaker than its younger counterpart, and is more likely to tear or suffer from overuse injury [9,10]. This is especially true if the aging tendon also suffers from pathological degenerative changes [11].

Cellular Changes

Many changes occur at the cellular level in an aging tendon. The tenoblasts transform into tenocytes (and occasionally vice versa) [11]. The volume density of tendon cells as well as the number of tendon cells per unit of surface area decrease. There is also a decrease in the plasmalemmal surface density. The tendon cells become longer, more slender, and more uniform in shape [12,13]. With age, the nucleus-to-cytoplasm ratio increases, and finally the main body of the cell is almost completely occupied by a long, thin nucleus [1] (see Figure 4-1).

The overall metabolic activity of tenoblasts decreases with age, most likely slowing the reparative ability of a tendon. There is a decline in the organelles participating in protein synthesis, particularly the rough endoplasmic retinaculum. Therefore, the ability to synthesize protein and amino acids decreases [12,14]. However, the rough endoplasmic retinaculum and Golgi apparatus can be still recognized at electron microscopy. The cytoplasm has high quantities of free ribosomes and the number of mitochondria is decreased, but they still have well-defined cristae. Lysosomes can be identified in varying numbers. With increasing age, and especially in pathologic conditions, tenocytes show increasing numbers and amounts of glycogen particles, lipid droplets, lipofuscin, and lysosomes [11]. Also, the metabolic pathways used to produce energy shift from aerobic to more anaerobic, and eventually some metabolic pathways such as the Krebs cycle completely shut down [11,15]. Reduced metabolic activity of the aged tendon has been recently shown in an *in vitro* model of a rat patellar tendon [16].

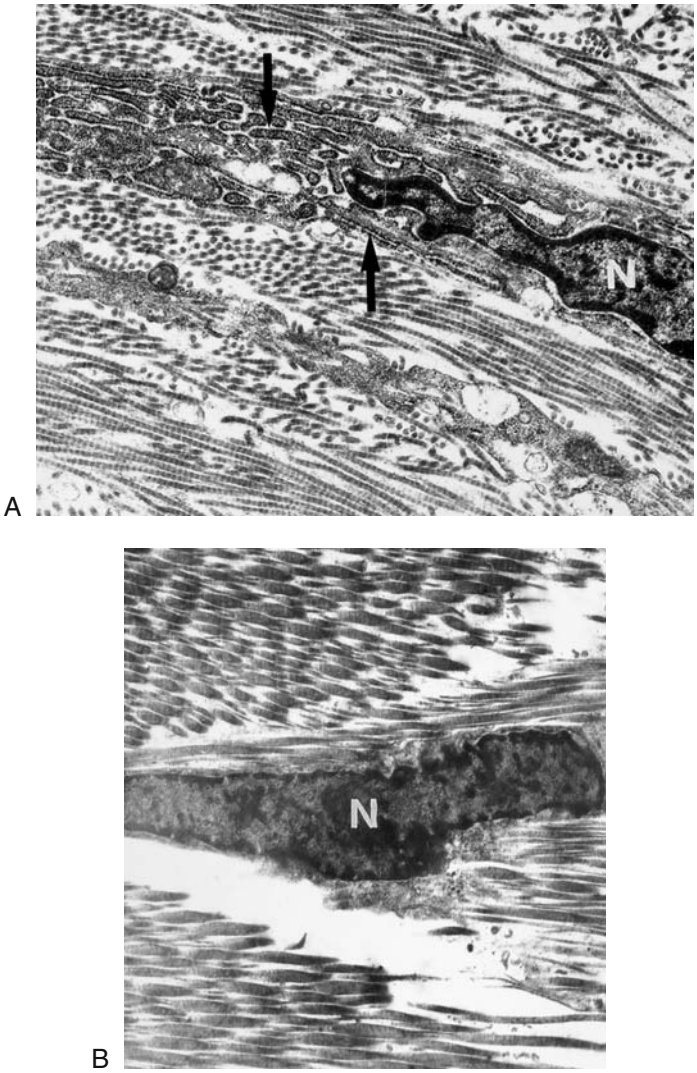

FIGURE 4-1. (A) A tenoblast with a well-developed, rough endoplasmic reticulum (arrows). N = nucleus. An intact Achilles tendon from a young adult cadaver (Transmission electron micrograph, TEM × 6600). (B) A tenocyte with a large nucleus (N) and high nucleus-to-cytoplasm ratio. An intact Achilles tendon from a traumatically amputed limb of an older adult (TEM × 6000).

Extracellular Changes

With development and aging, both the collagen and noncollagenous matrix components of tendons show qualitative and quantitative changes. The collagen content remains unchanged or decreases slightly to 75%, while the amount of proteoglycans and glycoproteins declines more intensely. The elastic components increase into early adulthood to decrease into old age. The extracellular water content of a tendon declines from about 80% to 85% at birth to approximately 30% to 70% in old age [11,15,17]. The decrease in water and mucopolysaccharide contributes to the age-dependent changes of stiffness of tendons and a reduction in their gliding properties [1,12].

Collagen

Within the tendon, the most remarkable age-dependent changes are those that involve collagen (see Figure 4-2).

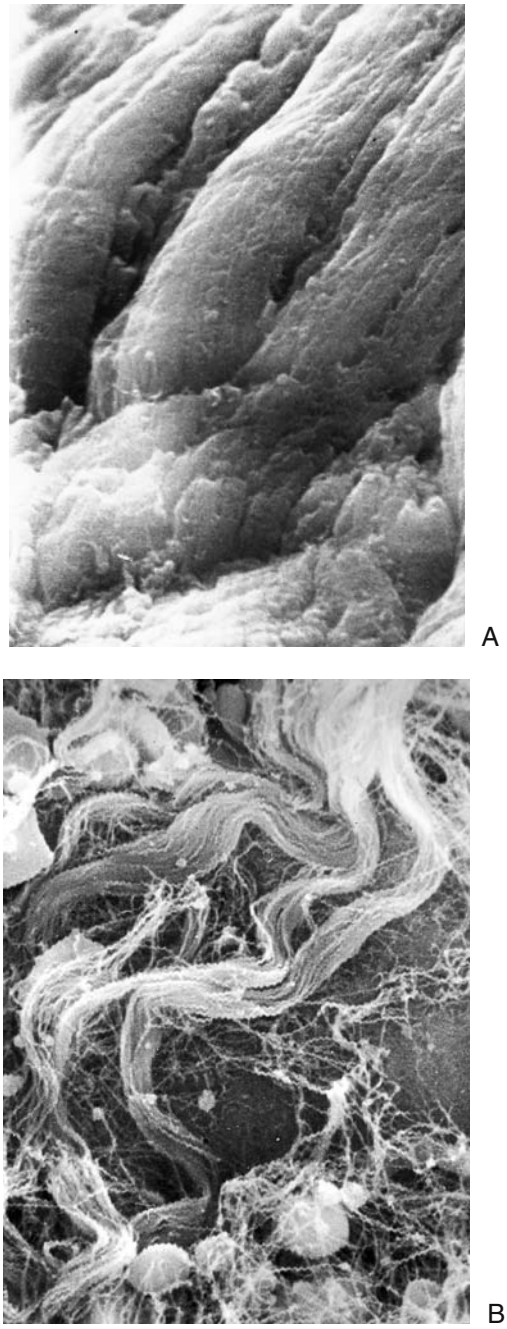

FIGURE 4-2. (A) Normal collagen bundles of an Achilles tendon of a young adult cadaver (Scanning electron microscope, SEM × 1700). (B) Disintegrated and frayed collagen bundles of an Achilles tendon of an older adult cadaver (scanning electron microscope, SEM × 1300).

With age, the absolute collagen content changes little, while the relative amount of collagen and the collagen volume density of the tendon increase due to decrease in the proteoglycan-water content. The type II collagen-containing region spreads significantly from the attachment zone of the tendon into the tendon substance [1,12,18,19]. The mean collagen fibril diameter shows a marked increase during development, while a decrease in the proportion of thick fibrils and in the mean area of the fibrils occurs with senescence [13]. Collagen turnover, which is relatively low to begin with, declines with age as collagen synthesis diminish [11,18]. Due to the age-dependent reduction of tendon cells and enzymes that are essential for collagen synthesis, repair of the soft tissues, such as tendon, is delayed in old age.

During senescence, the mechanical properties of collagen decrease [20]. This is due to changes in collagen crosslinking profile, as there is an increase in the crosslinking of the tropocollagen molecules decreasing the solubility of collagen [9,10]. The conversion to nonreducible crosslinks is a spontaneous age-related process, although mechanical stress and hormones may have an additional effect [1,21]. The increase in crosslinks has been observed to have an effect on several laboratory-detected phenomena: an increased resistance to degradative enzymes [22]; reduced solubility of collagen [2,19,23]; increased stability to thermal denaturation [2,23]; and increased mechanical stiffness [23,24]. The crosslinking of collagen is considered one of the best biomarkers of aging [25].

Elastin and Contractile Proteins

With increasing age, a decrease in the number of elastic fibers as well as many morphological changes have been observed [11,12,18]. These could be related to an increase in the synthesis of fibrillar glycoproteins associated with partial degeneration of elastin by tissue elastases [21].

The presence of the contractile proteins actin and myosin has been demonstrated in tendon cells, and these remained unchanged with age [12,17]. Anderson [26], however, found an increased actin content in old chick fibroblasts.

Other Noncollagenous Matrix Components

The extracellular water content and mucopolysaccharide content decrease with aging [2,9,12,19]. Total glycosaminoglycan and glycosaminoglycan fractions show a pronounced decrease during the maturation period. This trend continues, albeit to a lesser degree, during the rest of the life span [1]. Also, the composition of the glycosaminoglycans changes during aging, as the amount of dermatan sulfate (major component of glycosaminoglycans in tendons of newborns) decreases and chondroitin sulfate becomes prominent [27].

Blood Vessels

Tendon blood flow and the number of capillaries per unit of surface area decrease with increasing age [11]. The decreased arterial blood flow and thus decreased nutrition and oxygen transport have been suggested to be the main etiological factors behind the age-related tendon degeneration [28,29]. There are also numerous age-related pathological changes in the blood vessels of the tendon and its paratenon. (See section on age-related pathological changes below.)

Biomechanical Changes

The most drastic biomechanical change of tendon aging is decreased tensile strength [30]. The increase in collagen crosslinking widely alters the mechanical properties of the tendon as there can be found a decrease in ultimate strain, ultimate load, modulus of elasticity, and tensile strength, and an increase in mechanical stiffness [9,23,31]. The increased rigidity of collagen fibers results in a decrease in the tensile strength of a tendon [9]. It appears that there is an ideal amount of stabilized crosslinks beyond which more crosslinking stabilization becomes a maladaptive adjustment [9,23]. Other biomechanical tendon variables altered by aging are those associated with tissue viscosity, namely stress relaxation, mechanical recovery, and creep [31].

With age, the relative collagen content of a tendon increases, but the elastin and proteoglycan matrix decrease, suggesting less elasticity [11]. However, the pattern of change of the modulus of elasticity of tendon follows that of total collagen content and not of elastin [1].

Altogether, the above-noted changes make the tendon weaker than its younger counterpart and more likely to tear or suffer from overuse injury when subjected to increasing stress and strain [1].

Age-Related Pathological Changes

The most characteristic age-related microscopic and biochemical pathological changes are degeneration of the tenocytes and collagen fibers, and accumulation of lipids, ground substance (glycosaminoglycans), and calcium deposits [18]. These may occur separately or in combination, and very often these changes occur with changes in the blood vessels of the tendon or its paratenon. The vascular changes include narrowing of the lumina of the arteries and arterioles, usually due to hypertrophy of the intima and media of the vessel walls. Sometimes they are associated with deposition of fibrin, formation of thrombus, and evidence of proliferative arteritis, arteriolitis, and periarteritis [11] (see Figure 4-3). The decreased arterial blood flow and thus decreased nutrition and oxygen transport have been suggested as the main etiological and

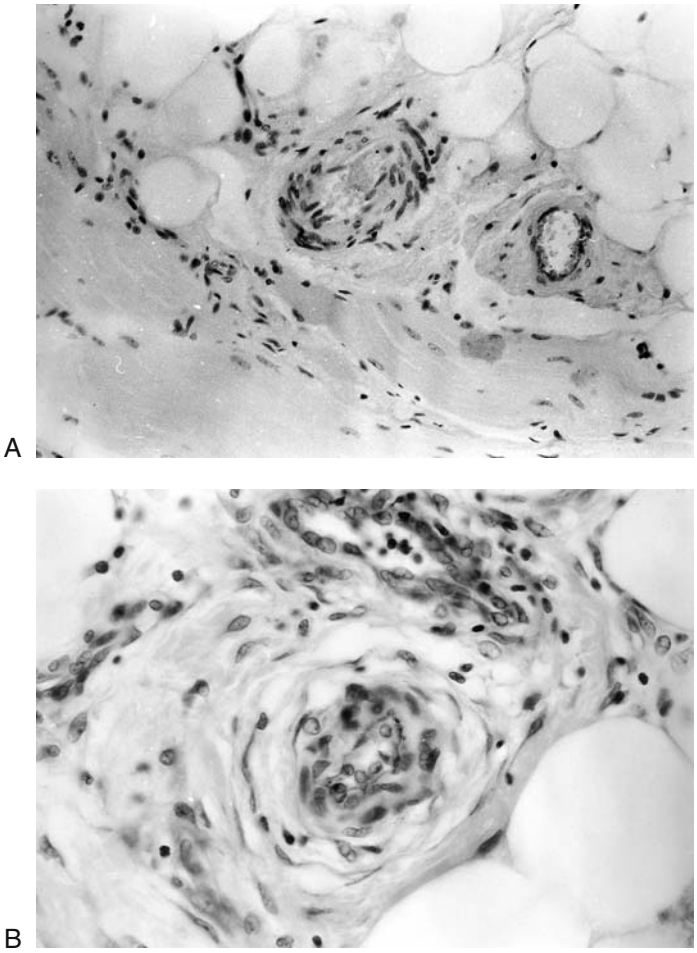

FIGURE 4-3. (A) Obliterative arteriopathy of a ruptured Achilles tendon. The vessel walls are thickened and the lumina narrowed (Hematoxylin-eosin, HE × 150). (B) Proliferative arteritis (middle) and phlebitis (above) of a ruptured Achilles tendon. The vessel walls are thickened and the arterial lumen almost obliterated (Hematoxylin-eosin, HE × 150).

pathogenetic factors behind age-related tendon degeneration [28,29], but direct evidence is still lacking.

Focal lipid deposits can be seen already at the age of 15 [32], but the process does not accelerate until the fourth decade of life [18]. The Achilles, biceps brachii, anterior tibial, and especially the quadriceps and patellar tendons are the most severely affected anatomic sites [32,33].

The most frequent form of lipid accumulation during aging is extracellular accumulation in which lipids with a high content of esterified cholesterol are spread along the axis of collagen fibers. These fine droplets are plasma low-density lipoprotein filtrates [11]. The effect of lipid deposition is to disrupt the fiber bundles and thus diminish tendon strength.

Areas of reduced blood flow and maximal lipid deposition correlate with the classical sites of tendon rupture, particularly those of the Achilles and posterior tibial tendons [28,34]. Tendon rupture is usually preceded by histopathological degenerative changes, including hypoxic degenerative tendinopathy, mucoid degeneration (Figure 4-4), tendolipomatosis (Figure 4-5), and calcifying tendinopathy, either alone or in combination, and

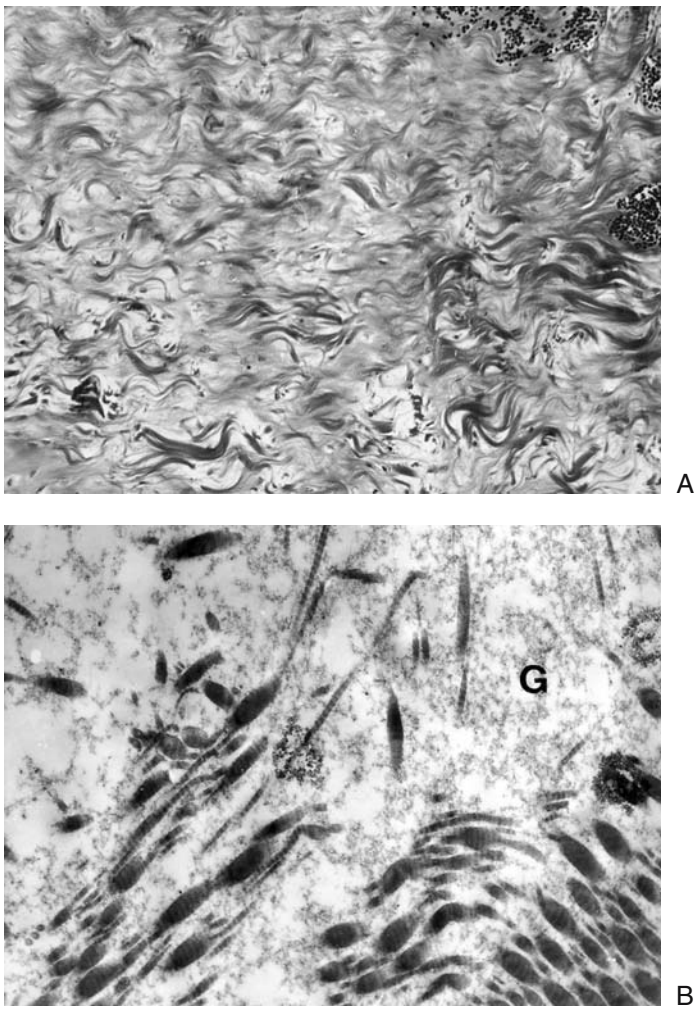

FIGURE 4-4. (A) Mucoid degeneration of a ruptured Achilles tendon. The collagen fiber structure is loose and disintegrated (Masson trichrome staining × 150). (B) Mucoid degeneration of a ruptured Achilles tendon. The collagen fibrils vary in diameter and run in various directions. Among the fibrils, large amounts of mucus-like fine granular material (glycosaminoglycans, G) is visible (TEM × 8300).

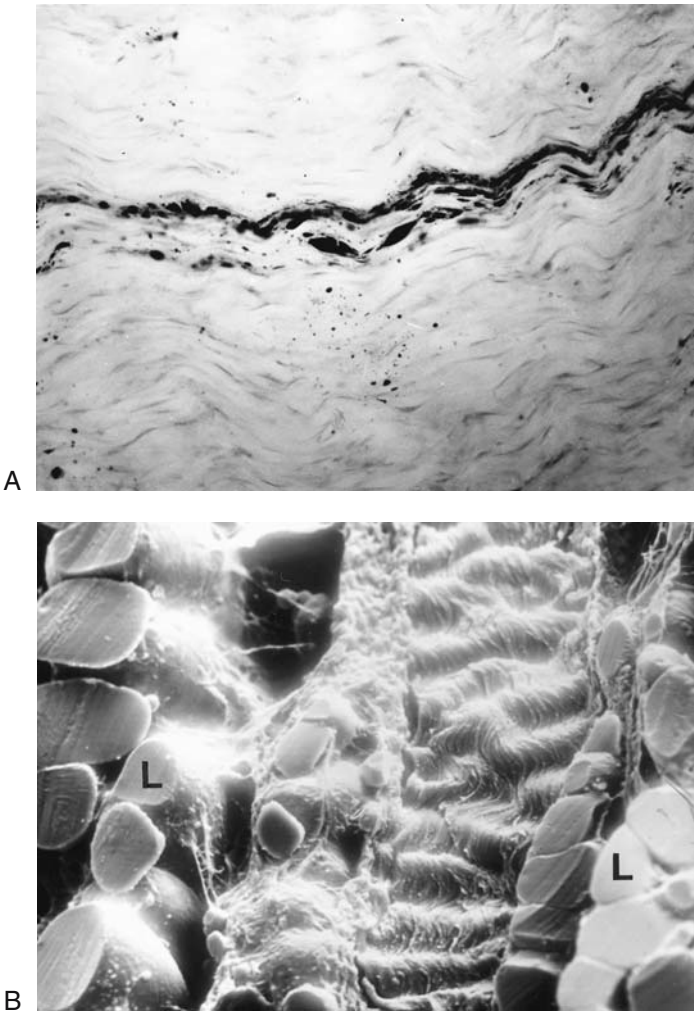

FIGURE 4-5. (A) Tendolipomatosis of a ruptured Quadriceps tendon. Lipid cells (black) have accumulated between the collagen fibers forming long chains (Sudan Black staining × 100). (B) Tendolipomatosis of a ruptured Quadriceps tendon. Lipid cells (L) have accumulated between the collagen fibers (SEM × 870).

the incidence of these degenerative changes tends to increase with age [18,35]. In patients with Achilles tendon rupture, aging has been shown to be associated with many complications after surgical and nonsurgical treatment [35]. In shoulders, in turn, rotator cuff lesions, detected by ultrasonography, are suggested as a natural correlate of aging, with a statistically significant linear increase in asymptomatic partial- or full-thickness tears after the fifth decade [36].

In clinical practice, the most disconcerting and irritating problem of tendinopathies is pain rather than the age-related pathological changes of tendon. Traditionally, the pain associated with chronic tendinopathy has been assumed to arise through one of two mechanisms: inflammation or separation of collagen fibers [37,38]. However, neither of these classical hypotheses holds up under scientific scrutiny [37–39]. As an alternative explanation for the origin of pain in chronic tendon disorders, it has been recently presented that as yet unidentified biochemical noxious compounds could irritate the pain receptors in the diseased tendon tissue [37,38]. Candidates include matrix substances, such as chondroitin sulfate or nociceptive neurotransmitters, such as substance P. However, before any extended conclusions, much future research is needed to clarify the possible cause-and-effect relationships between these candidate substances and the tendon pain.

Factors Influencing the Rate of Aging and Prevention of Age-Related Tendon Degeneration

The rate of aging is highly individual and can be influenced by many factors, including genetics, lifestyle, hormonal changes, and disease processes [9]. Thyroxine is necessary for normal development: hypothyroidism causes an accumulation of glycosaminoglycans in the connective tissue throughout the body [1]. Corticosteroids are catabolic and, especially at moderate to high pharmacological levels, they inhibit the production of new collagen. Insulin, estrogen, and testosterone increase the production of collagen to varying degrees by preventing excessive collagen breakdown [10]. Hamlin et al. [40], for example, showed that collagen from 40-year-old diabetics corresponds to that of normal individuals at 100 years of age. Nutritional deficiencies can also be associated with tendon degeneration. Adequate food supply of proteins is needed for the necessary amino acids of collagen and other proteins, and of carbohydrates for the maintenance of the ground substance.

Tendons are altered structurally and chemically by activity, and even more so by inactivity. Exercise appears to have a beneficial effect on aging tendons [11,41]. Long-term exercise increases the mass, collagen content, cross-sectional area, ultimate tensile strength, weight-to-length ratio, and load-to-failure of tendon tissue [11,24,42–44]. Although these positive effects of exercise on tendon properties are relatively small, the rate of degeneration with age can probably be reduced by regular activity. Sedentary lifestyle, in turn, is probably one of the main reasons for poor circulation in tendons [18]. On the other hand, some elderly athletes suffer from overuse-related and degenerative sports injuries, including tendinopathies.

In clinical practice, to prevent age-related tendon degeneration and related symptoms, maintenance of flexibility and neuromuscular coordination through daily stretching and calisthenics is recommended. Long warm-

up and cooling-down periods should be the rule. The advice about slow increase in the intensity, duration, and frequency of training is especially suitable for elderly people. Finally, special attention and caution should be paid to sports in which the lower extremities are fully weight-bearing with strong impacts and quick acceleration and deceleration movements, such as running and fast ball games with repeated jumping. Thus, particularly in elderly athletes, participation in sports like swimming, cycling, and walking, in which the whole body weight is not on the lower extremities or the impact effects and muscle forces are lower, is recommended.

Summary

The changes associated with increasing age result in a decline in the structure and function of human tendons. Age correlates with decrease in the number of tenoblasts and overall tenoblastic activity. Structurally, collagen fibers increase in diameter, vary in thickness, lose tensile strength, and become tougher with increasing age and so the ultimate tensile strength of a human tendon declines.

Age also affects tendon blood flow and the number of capillaries per unit of surface area. The most characteristic age-related microscopic and biochemical pathological changes are degeneration of the tenocytes and collagen fibers, and accumulation of lipids, ground substance (glycosaminoglycans), and calcium deposits.

Careful control and treatment of nutritional deficits and altered hormone levels, whether due to disease or pharmacological intervention, may reduce the harmful aging effects on tendon tissue. Also, participation in a well-structured, long-term exercise program may minimize or retard the effects of aging on tendons.

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