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Growth and Development of Tendons

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Introduction

Tendons appear in the mesenchyme of the limb bud at 6 to 8 weeks of fetal life and join with the muscles originating from the somites. They are initially very cellular but become less so throughout growth to adulthood as matrix elements are synthesized. Their collagen fibrils become larger in diameter during maturation while the tendons are also gaining in cross section. Longitudinal growth is diffuse, rather than occurring at a growth plate as in bone, and the mechanism of this growth appears to involve the sliding of collagen fibers or fibrils past one another.

Fetal Formation

Tenocytes originate from the somatopleure which differentiates into the mesenchyme that forms the embryonic limb bud. The subsequent development of the tendons requires the presence of muscle tissue originating in the somites. If the somites are destroyed by radiation, tendon development ceases [1].

For the most part, fetal tendons consist of Type I and Type III collagen fibrils, proteoglycans, and tenocytes (fibroblasts). Fetal collagen fibrils are small in diameter (10 to 30 nm). Fetal tendon is very cellular as compared to mature tendon, having as many as 200 000 cells per mm^3. Between 6.5 and 8 weeks into the development of the embryo, tendons can be first detected at the ends of the fetal muscle bellies. Upper extremity tendons develop more rapidly than lower extremity tendons, and flexor tendons develop more rapidly than extensor tendons.

Changes During Postnatal Growth

Changes in Cellularity

At birth tendons are highly cellular, having 200 000 cells per mm^3. The cellularity drops rapidly during the first five years of life to approximately 100 000 cells per mm^3. The cellularity continues dropping, reaching about 50 000 cells per mm^3 by age 15 to 20 [2]. The cellularity is so high that in newborns the cell-to-matrix ratio appears to be one-to-one [3]. During growth, as the cellularity decreases, the tenoblasts become tenocytes. They become longer and more slender, and their cytoplasmic processes elongate, forming a dense network around and through the surrounding collagenous matrix. As the tendon matures, there is a decrease in the numbers of the intracellular organelles responsible for protein synthesis [4].

Changes in the Matrix

With the decrease in cellularity of the growing tendon, it is obvious that there is relative increase in the amount of matrix. Collagen fibril diameters increase during growth. In the fetus and the newborn, most fibrils are 40 nm in diameter or smaller, whereas in more mature tendons much larger diameters are represented, ranging up to 500 or even 600 nm [5]. With growth there is no increase in the number of elastic fibers contained within the tendon. Water content drops from 75% in the newborn to 61% in the young animal, and mucopolysaccharide content drops as well.
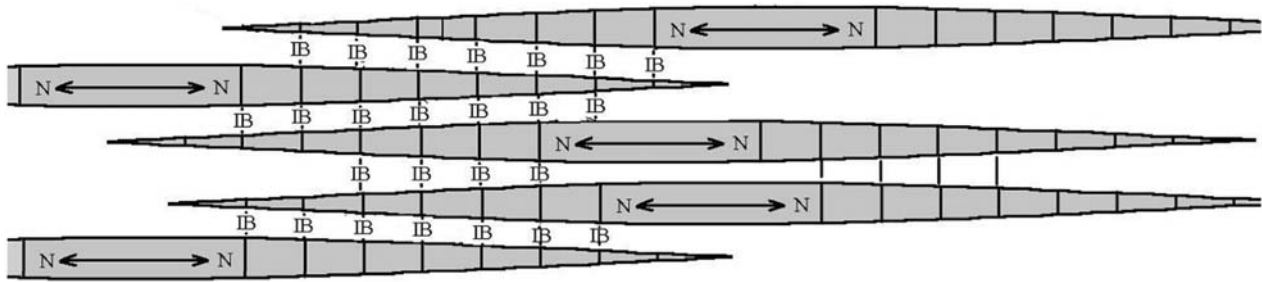
FIGURE 3-1. Collagen fibrils are represented here in gray. They taper to points on both ends, and the ends are apparently mostly amino terminal. These are not drawn to scale, as collagen fibrils in rat are 300 to 500 times as long as their radius. "IB" repre- sents the presumed interfibrillar bonds, which are thought to be temporarily released to allow fibril sliding during elongation of the tendon during growth.

Cross-Sectional Growth

The cross-sectional area of tendon increases in a rela- tively linear fashion from birth through puberty. At birth, the tendon of the biceps brachii has a cross-sectional area of about $8\,mm^2$ and the area increases linearly, reaching approximately $37\,mm^2$ by age 20, when the growth curve flattens out [6]. In ligament, there is evidence that much of the new tissue formed to increase diameter is laid down by surface cells (so-called "periligament") [7], and it seems likely that a similar mechanism is involved in increasing the diameter of tendons.

Longitudinal Growth

Marker studies using sutures in growing animals have demonstrated that longitudinal growth occurs intersti- tially throughout the length of tendons rather than at a "growth plate" or area as occurs in bone. While Crawford [8] found increased growth at the muscle-tendon junction in rabbits, Nishijima et al. [9,10] did not find this phe- nomenon in their studies of the rabbit or chicken muscle tendon junction. Nishijima felt that longitudinal tendon growth in an area corresponded to the amount of growth in the underlying bone. Such diffuse interstitial growth most likely occurs through the sliding of fibrils or bundles of fibrils past one another. As they slide so that they overlap less, the tendon is lengthened. This presumably occurs through the release of reversible interfibrillar bonds with their reattachment after the fibrils have fin- ished sliding (see Figure 3-1). These reversible interfib- rillar bonds have been postulated to involve the decorin molecules which "decorate" the surface of collagen fibrils. NKISK, a competitive inhibitor of the binding of decorin to fibronectin (a molecule which frequently fills the role of tissue adhesive) has been shown to potentiate creep in rat tail tendons. Tendons that have been stretched in the presence of NKISK have been demonstrated to undergo sliding of fibrils or bundles of fibrils [11]. Such sliding of fibrils has been documented *in vivo* in growing and in contracting ligaments, but not in tendon [12].

Fetal Tendon Tissue Response to Injury

Fetal tissue in the early to mid-gestational stage responds to injury in a fundamentally different manner than does adult tissue. In general, fetal wound healing occurs at a faster rate and in the absence of scar formation [13]. Fetal tendon tissue undergoes scarless, regenerative healing [14]. The basis for the ability of fetal tissues to heal without scarring remains unknown. The regenerative response of fetal tissues is intrinsic to the tissues them- selves, not of the fetal environment [15]. It is therefore possible that biologic modulation of tendon tissue repair potentially could lead to a regenerative healing process in adults [16,17], but the application of these ideas in clinical practice is still in the future.

References

1. Kieny M, Chevalier A. (1979) Autonomy of tendon devel- opment in embryonic chick wing. *J Embryol Exp Morphol.* 49:153–165.
2. Ingelmark BE. (1948) The structure of tendon at various ages and under different functional conditions. *Acta Anat.* 6:193–225.
3. Jozsa L, Balint BJ. (1977) Development of tendons during the intrauterine life. *Traumatologia.* 20:57–61.
4. Ippolito E, Natali PG, Postacchini F, Accini L, De Martino C. (1980) Morphological, immunochemical, and biochemi- cal study of rabbit Achilles tendon at various ages. *J Bone Joint Surg* (Am). 62A(4):583–598.
5. Moore MJ, De Beaux A (1987) A quantative ultrastructural study of rat tendon from birth to maturity. *J Anat.* 153: 163–169.
6. Jozsa L, Kannus P. (1997) Embryonal and postnatal devel- opment of tendons and their disturbance. In: Jozsa L, Kannus P, eds. *Human Tendons: Anatomy, Physiology, and Pathology*. Champaign, IL: Human Kinetics; 114–126.

7. Frank C, Bodie D, Anderson M, Sabiston P. (1987) Growth of A Ligament. Orthopaedic Research Society, 33rd Annual Meeting, San Francisco.

8. Crawford GNC. (1950) An experimental study of tendon growth in the rabbit. *J Bone Joint Surg* (Br). 32B(2): 234–242.

9. Nishijima N, Yamamuro T, Ueba Y. (1994) Flexor tendon growth in chickens. *J Orthop Res*. 12:576–581.

10. Fujio K, Nishijima N, Yamamuro T. (1994) Tendon growth in rabbits. *Clin Orthop*. 307:235–239.

11. Wood ML, Luthin B, Lester GE, Dahners LE. (2000) Creep in tendons is potentiated by a pentapeptide (NKISK) and by relaxin which produce collagen fiber sliding. *Trans Orthop Res Soc*. 25:61.

12. Wood ML, Lester GE, Dahners LE. (1998) Collagen fiber sliding during ligament growth and contracture. *J Orthop Res*. 16:438–440.

13. Adzick NS, Longaker MT. (1992) Scarless fetal healing: therapeutic implications. *Ann Surg*. 215:3–7.

14. Rowlatt U. (1979) Intrauterine wound healing in a 20 week human fetus. *Virchows Arch A Pathol Anat Histol*. 381: 353–61.

15. Flanagan CL, Soslowsky LJ, Lovvorn HN, Crombleholme TM, Adzick NS. (1999) A preliminary comparative study on the healing characteristics of fetal and adult sheep tendon. *Trans Orthop Res*. 24:1080.

16. Lorenz HP, Lin RY, Longaker MT, Whitby DJ, Adzick NS. (1995) The fetal fibroblast: the effector cell of scarless fetal skin repair. *Plast Reconstr Surg*. 96:1251–1259.

17. Peled ZM, Rhee SJ, Hsu M, Chang J, Krummel TM, Longaker MT. (2001) The ontogeny of scarless healing II: EGF and PDGF-B gene expression in fetal rat skin and fibroblasts as a function of gestational age. *Ann Plast Surg*. 47:417–24.