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A biodegradable composite artificial tendon

P. A. DAVIS*, S. J. HUANG
Institute of Materials Science, University of Connecticut U-136 Storrs, CT 06268-3136, USA
L. AMBROSIO‡, D. RONCA§, L. NICOLAIS
Department of Materials Production and Engineering, University of Naples, Piazzale Tecchio, Naples 80125, Italy

The development of a completely biodegradable composite artificial tendon prosthesis that mimics the structure and stress–strain response of natural tendon is presented. The artificial tendon is a composite of water-swollen poly(2-hydroxyethylmethacrylate)/poly(caprolactone) blend hydrogel matrix reinforced with poly(lactic acid) fibres.

1. Introduction

Biomedical implants serve as the last resort to surgically solve difficult and chronic medical problems. Synthetic polymers make up most of these implantable devices due to their vast range of properties and diversity. Early tendon implants were designed only from homogeneous and biologically inert materials intended to permanently replace damaged tendons. Biocompatibility and biostability were major requirements for these prostheses.

Adequate mechanical properties are important for implant function. It is extremely difficult to find materials with appropriate biological and mechanical properties. A solution to this dilemma is to use those which, in fact, degrade slowly after implantation as the body heals itself and to combine the few available biocompatible materials into composites tailored to the mechanical characteristics of the prosthesis.

Prosthetic materials have been used for surgical repair of tendons as early as 1914 [1]. Despite enormous effort, the difficulties involved in providing successful tendon repair remain to this day. Since failure in tendon repair surgery makes up a large percentage of the cases attempted, there is a gradual shift toward understanding tendon healing process and fitting the material design requirements of the implant to the short-term needs of the system. This approach avoids the need to meet long term arduous and unrealistic material design demands.

Tendons are principally composed of fibrous collagen embedded in a gel-like acid mucopolysaccharide matrix [2, 3]. They transmit tensile loads from muscle to bone [4] and are designed to undergo considerable extension and support large tensile forces. Bundles of the collagen in the matrix are surrounded by an outer sheath. There are innumerable studies on the structures and mechanical properties of natural tendon [2, 4–16]. However, knowledge of tendon properties is still inconclusive.

The work of Dale and Baer [9] on rat tail tendon verified this wave structure in other mammalian tendons, while noting that tendon deformation in the physiological range is primarily a result of the straightening of this waveform into a parallel pattern. This particular ultrastructure yields a unique type of stress–strain curve (shown in Fig. 1), consisting of three regions. First, there is a toe region, followed by a linear region, then a yield and failure region [4]. The toe region reflects the straightening of the waves to the oriented pattern. The linear region results from extension of the collagen fibres. Although deformation in the yield and failure region is partly by irreversible damage to the collagen fibrils that causes alteration of the waveform.

Dale and Baer [9] proposed that the planar waveform structure of natural tendons results from a compressive buckling mechanism which in turn originates from interaction between collagen fibres and the mucopolysaccharide matrix. They re-created this effect in a composite of nylon fibres in a poly(ethyl acrylate) matrix. The procedure was essentially the polymerization of the matrix around the fibres accompanied by a 20% volume shrinkage. More recently, Sanchez De La Asuncion and colleagues [10] repeated this effect with crimped poly(ethyleneterephthalate) (PET) fibres in a poly(methyl methacrylate) (PMMA) matrix.

The accepted structure of natural tendon is a highly complex structural hierarchy. The smallest structural part is called tropocollagen which combine to make up the microfibrils that, in turn, constitute the subfibrils. The structure continues from the subfibrils to the fibrils onto the fascicles. Fascicles are responsible for the waveform described earlier. Lastly, the natural tendon in its integral form is composed of bundles of fascicles.

Torp *et al.* [4] remarked on the non-linear viscoelastic stress–strain behaviour of rat tail tendons and drew an analogy between natural tendon and syn-

* Present address: Bascom Palmer Eye Institute, 1638 N.W. 10th Avenue Miami, FL 33136, USA.
‡ Present address: Institute of Composite Materials Technology, CNR, University of Naples, Piazzale Tecchio, Naples 80125, Italy.
§ Present address: School of Medicine I, University of Naples, Via S. Andrea della Dame 4, Naples 80122, Italy.

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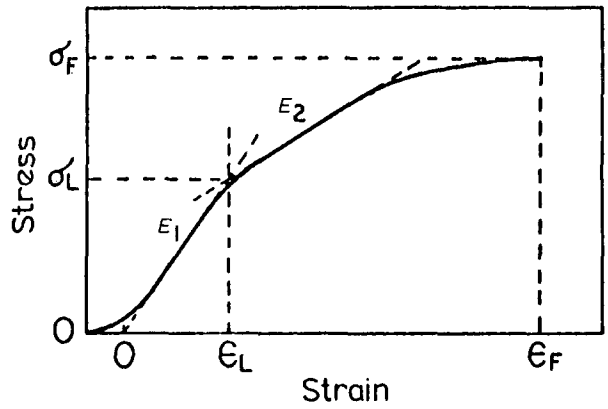

Figure 1 Unique type of stress–strain curve of natural tendon. There are three distinct regions: a toe region, a yield region, and a failure region [4].

thetic polymer in their mechanical behaviours. As a result, many authors have turned to composite technology to model and understand the mechanical behaviour of natural tendon. The accepted model for predicting the linear yield and failure regions (shown in Fig. 1) is a simple composite of uniaxially oriented fibres embedded in a viscoelastic matrix. The fibres support stress while the matrix holds them together.

Major problems are encountered during the tendon healing process [18–34]. Recovery of tendon function requires differential wound healing. This takes place after the production of scar tissue. The early part of the healing process usually results in tying the tendon to its unyielding, fixed sheath. The newly produced collagen fibrils must be remodelled into the common polarized pattern of normal tendon collagen.

Prosthetic devices in tendon repair fall into three major categories: blocking agents [28–34], pseudosheaths [22, 35–39], and artificial tendons [30–35, 40–57]. Artificial tendons have been used primarily in the past as temporary tendon replacement until neosheath generation [30–35]. Still, long-term use of artificial tendons has been attempted for many decades. Many different types of materials were tried, most of which were polymeric. At first, inert biocompatible elastomers such as silicone became popular; but today the impetus is to design composite tendons. Continuous fibres are placed in a matrix in such a manner that the strength, flexibility, and/or microstructure of the prosthesis closely matches those of the natural tissue.

Examples of early digital flexor tendon replacement protheses were described by Sarkin [40], Williams and August [41] and Bader and Curtin [42]. Materials used were nylon filaments covered with polyethylene, (PE), tube [40], woven Teflon [41, 42].

Extensive work has been reported on absorbable polymer-carbon composite tendon replacement by Alexander *et al.* [48–52]. Infections from migrating carbon particles remained a problem with testing these implants. None the less, new collagen fibres developed and aligned in the direction of the carbon fibres.

Another composite tendon, composed of polyester fibres, was developed by Migliaresi and Nicolais [53]. The composite was prepared by placing crimped PET fibres in a crosslinked swollen PHEMA matrix. A most important result of crimping the fibres is that the artificial composite tendon structure matches the ultrastructure of natural tendon [54]. Preliminary implantation results showed collagenous growth orientated along the fibres and degradation of PHEMA [55].

A PHEMA/collagen composite tendon [56] described by Stol *et al.* displayed excellent biological acceptance and mechanical stability. However, later implantation results reported by Cifková *et al.* [57] revealed that the composite is prone to calcification some 6–12 months after implantation. The degree of calcification of the implant depended on the collagen content.

The investigations of Alexander *et al.* [48–52] and Migliaresi *et al.* [53–55] used the concept of tissue scaffolding. The synthetic devices provided mechanical integrity and absorbed the mechanical load of the tendon during the time when collagenous tissue grew in and around the implant. Then, depending on the conformation of fibres present, the mechanical load was transferred over time to the regrown tissue as the device fatigues. Devices to date so far have limited success.

We report here our results on a poly(2-hydroxyethyl methacrylate)/poly(caprolactone) gel reinforced with poly(lactic acid) fibre composite tendon. This absorbable prosthesis is expected to degrade over a period of six to nine months as new tissue grows in to replace it.

2. Experimental

2.1. Materials

A chloroform of solution 2-hydroxyethyl methacrylate (HEMA) (from Polysciences) was washed with aqueous $NaHCO_3$, water, then dried over anhydrous $MgSO_4$. Distillation at 65 °C under 0.3 mmHg with 2,2′-diphenyl-1-picryl-hydrazyl as stabilizer resulted in pure HEMA. Poly(caprolactone) (PCL) (from Union Carbide) was purified by precipitation from ethyl acetate solution with ethanol. 2,2′-azobisisobutyronitrile (AIBN) (from Du Pont) was recrystallized from aqueous ethanol. Ethylene dimethacrylate (EDMA) was obtained from Polysciences.

2.2. Methods

2.2.1. Tendon preparation

Poly(lactic acid) in the form of Davis & Geck 5-0 Dexon Plus™ fibre was wound helically back and forth on a filament winder until a fibre braid was obtained. The fibre was coated simultaneously with the matrix prepolymer solution of PHEMA/PCL (90/10), 0.5 wt % EDMA, and 0.1 wt % AIBN. The braided fibre was inserted into a Teflon™ tube filled with the prepolymer solution, then sealed in clipped silicone tubing. Polymerization at 90 °C for 1 h yielded the cured tendon.

2.3. Analysis techniques

2.3.1. Static mechanical analysis

Swollen artificial composite tendons were tested in tensile mode on an Instron Universial Tester, Model 4301, at room temperature along with explanted natural achilles tendons for comparison. A strain rate of 0.1 min^{-1} was used. Tensile stress was correlated with the initial cross-sectional area of the sample.

2.3.2. In vivo implantation

Artificial tendon prostheses were implanted into the achilles heel of white rabbits. A 2.5 cm long section of the implant was sutured to severed rabbit achilles tendon. The leg of the animal was kept immobile for 45 days after which explantation of the tendon was preformed. The explanted tendon and adjacent tissue were analysed histologically. Body temperatures of the animal was monitored and recorded twice daily for signs of infections.

3. Results and discussion

Earlier work [55] has shown that water swollen PHEMA has low strength and tear resistance. A phase separated PHEMA/PCL blend was created so that the water swollen PHEMA networks are "anchored" by the hydrophobic PCL particles resulting in a much stronger hydrogel [58]. Composite tendons of this strengthened hydrogel reinforced with crimped Dexon Plus™ fibres, configured similarly as in an earlier PHEMA-PET tendon [55], were then prepared. The degradation lifetime allows for the regeneration of the natural tendon. These mimicked the stress–strain behaviour of natural tendon shown in Fig. 1.

Fig. 2 is a collage of the different types of artificial tendons prepared from the 5–0 Dexon Plus™ fibres and the PHEMA/PCL 90/10 matrix. Tendon outer diameters (OD) ranges from 3 to 4 mm and some were prepared with variable internal diameter (ID) inner annuli. Instron testing of these tendons in the water swollen state after sterilization with ethylene oxide resulted in stress–strain curves displaying variable toe regions. In short, we were able to manipulate the size of the toe regions by changing the OD/ID ratio of the tendon.

Fig. 3 is a comparison of the stress–strain curves of natural tendons and the artificial tendon prostheses. The natural tendons were explanted from the achilles of a white New Zealand male rabbit and Instron tested within 1 h and seven days after explantation. The artificial tendons were prepared with different diameters and with and without internal holes of various sizes. The toe regions of the natural tendon vary, within the physiological range of 3–5% strain. The "aged" natural tendon was stored in formaldehyde and kept refrigerated during the time between explantation and testing. Ageing took place in the natural tendon tested after seven days due to cross-linking and embrittlement of the mucopolysaccharide matrix. The toe regions of the artificial tendons vary from 6 to 60% strain. Effort to reduce the ID by changing the filament winding angle to limit the toe region to the physiological range is in progress.

Fig. 4 has stress–strain curves of one of the PHEMA/PCL 90/10–5-0 Dexon Plus biodegradable artificial tendon prosthesis and the fresh natural tendon. This prosthesis has a diameter of 4.9 mm and has no internal hole. It is the tendon used in the first implantation experiments. One notable aspect of

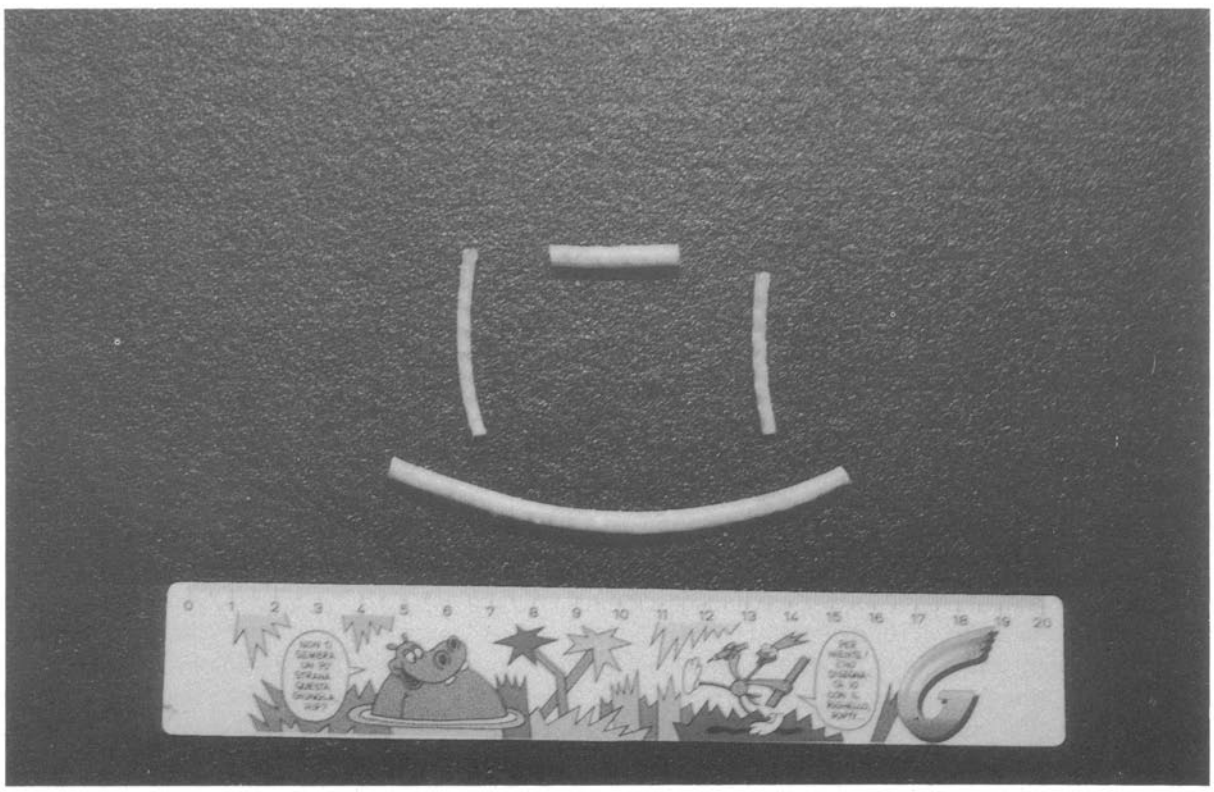

Figure 2 A collage of the different types of biodegradable composite artificial tendon prostheses.

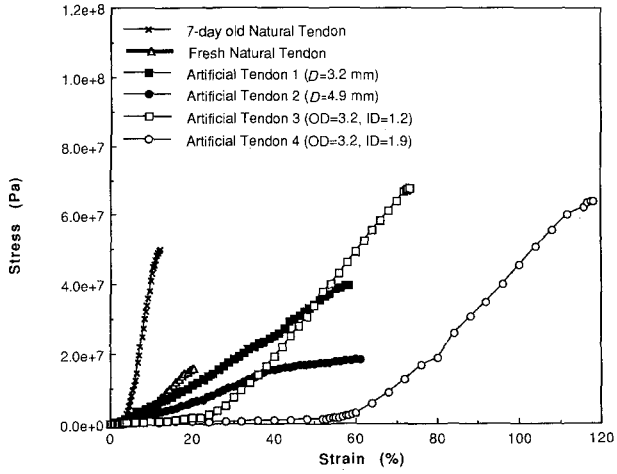

Figure 3 Stress–strain curves of natural and artificial tendons.

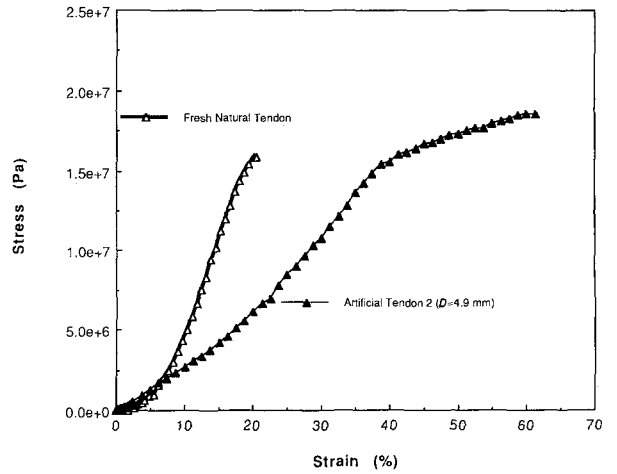

Figure 4 Stress–strain curves of one of the biodegradable composite artificial tendon prosthesis and natural tendon. This particular prosthesis was implanted into the achilles of the rabbit for 45 days.

Fig. 4 is the similarity in static mechanical behaviour between the natural and artificial tendons in the toe regions of the stress–strain curves. Thus, we wish to assert that we have prepared a tendon prosthesis that mimics the stress–strain behaviour of natural tendon in the early parts of straining. The toe region is very important because it is the range of physiological motion. Natural tendon operates for the most part in the toe region by uncrimping and crimping of the collagen fibres as described earlier. Only in extreme cases will tendon function depart from the toe region. Therefore, having an artificial tendon with similar properties in the toe region is of utmost importance for mimicking the behaviour of natural tendon.

Fig. 5 is a photograph of the biodegradable artificial composite tendon prosthesis after 45 days of implantation into the achilles of the rabbit. The position in which the implant is held shows that it is intact, well connected to the tissue to which it is sutured, and acts very well as a load transmitter. There are no visible scar tissue indicating the absence of negative response. Recall that usually, as is explained above, tendon repair is hampered by gross scar tissue formation. This is not the case for the PHEMA/PCL-DEXON tendon prosthesis. Further examination of the surrounding

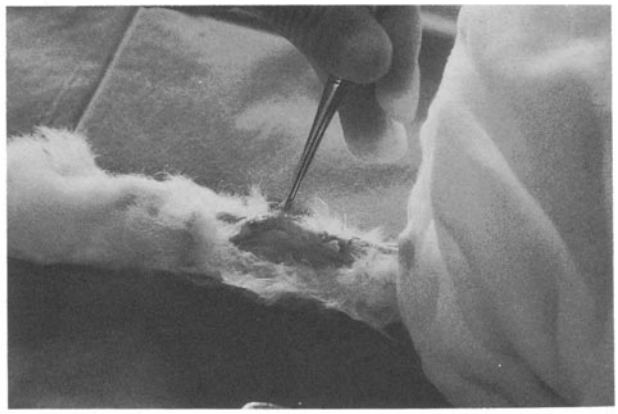

Figure 5 A picture of the biodegradable composite artificial tendon prosthesis implanted into the achilles of the rabbit for 45 days shortly before explantation.

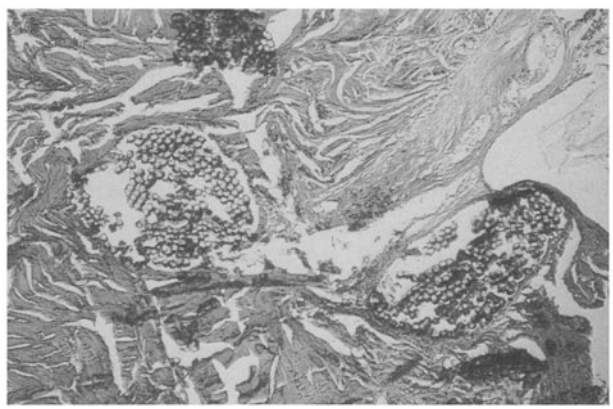

Figure 6 A picture of a cross-sectional histological section of the explanted tendon prosthesis (mag. = 100×). This section shows the invasion of new connective tissue into the implant.

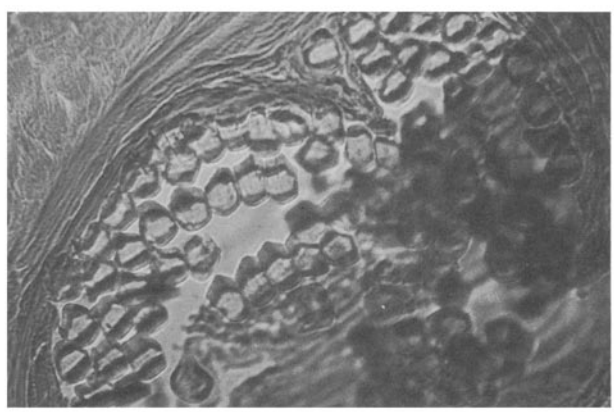

Figure 7 A picture of a cross-sectional histological section of the explanted tendon prosthesis of Fig. 6 at a higher magnification (mag. = 500×). This section shows the invasion of new connective tissue into the implant.

tissue and points of contact of the tendon implant shows no discolouration or sign of rejection activities such as inflammation or cell necrosis. The body temperature of the rabbits remained normal throughout the implantation period.

The tendon shown in Fig. 5 was explanted and analysed histologically. Fig. 6 is a cross-sectional

histological section of the tendon seen at a magnification of 100×. First and foremost, this picture indicates excellent implant tolerance by the surrounding tissue. No inflammation reaction is evident. Moreover, some very compact newly formed connective tissue (red in photograph) is apparent. This new tissue is invading the areas of the implant once occupied by the resorbing Dexon Plus fibres. Fig. 7 is a higher magnification (500×) of the same area. A fibre bundle is resorbing as new connective tissue grows into the area.

Three comments are appropriate from these latter figures (Figs. 5–7). First, we have shown that the biodegradable composite artificial tendon prosthesis is composed of resorbable materials that do not trigger any toxic nor negative reaction around the implant area. Secondly, the tendon performed as it should when placed *in situ*. In other words, it transmits load from muscle to bone. The implant is functional. Lastly, the resorption of the 5-0 Dexon Plus fibres is accompanied by the ingrowth of newly formed connective tissue. Future work in this area will ascertain if the new tissue differentiates, as is expected, into functional tendon collagen.

4. Conclusions

The history of prosthetic materials in tendon repair involves many different materials with few standout successes [59]. Polymers have played a major role because of their relative inertness and flexibility to be processed into various forms. Recent developments are attempts to mimic the structural hierarchy of natural tendon in a prosthesis that performs its function on a temporary basis. As the new tissue regrows, the temporary scaffold slowly resorbs. This concept appreciates the regenerative capacity of natural tissue and attempts to invoke differentiation and return of function without scar tissue proliferation or prolonged immobilization, which can inhibit the return of tendon function.

The successful development of a completely biodegradable composite artificial tendon prosthesis fabricated from a water-swollen PHEMA/PCL blend hydrogel matrix and 5-0 Dexon Plus degradable suture fibres was discussed. The fibres are filament wound to mimic the structural heirarchy of the natural tendon in a simplified manner. The unique property of this artificial tendon is the presence of a toe region on the stress–strain curve which is fairly similar to that of the natural tendon.

In vivo implantation of the prosthesis into the achilles of white New Zealand male rabbits was well accepted by the cells in that region of the body. No inflammation was noted. And more importantly, the start of the degradation of the fibre and matrix with ingrowth of new and differentiated collagenous material was histologically documented after 45 days. Extended inplantations are in progress.

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