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Tendon-to-bone tunnel healing in a rabbit model: the effect of periosteum augmentation at the tendon-to-bone interface

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Abstract We examined whether periosteum enhances the healing process of a tendon in a bone tunnel and leads to better biomechanical fixation in a shorter period of time. The effect of the periosteum-wrapped tendon on tendon-to-bone healing was analyzed in 20 New Zealand white rabbits. The animals were divided into two groups, a periosteum-wrapped group and a control group. The two legs were operated on in the same manner. The long digital extensor tendon was harvested and transplanted into the proximal tibial tunnel. One limb was transplanted with the tendon wrapped with periosteum, while the other was without periosteum. The healed tendon-bone attachment was evaluated after 3 and 6 weeks by histological examination and biomechanical testing. At all time points histological examination demonstrated more extensive bone formation around the tendon with closer apposition of new bone to the tendon in the periosteum-wrapped limb than in the control limb. Biomechanical testing demonstrated higher tendon pullout strength in the periosteum-wrapped limb at all time points, with statistically significant differences between the periosteum-wrapped limb and the control limb after 3 and 6 weeks. Histological and biomechanical data suggest superior healing at the periosteum-wrapped side. These findings demonstrate that periosteum enhances the healing process when a tendon graft is transplanted into a bone tunnel.

Keywords Periosteum · Bone tunnel · Tendon

Introduction

In anterior cruciate ligament (ACL) reconstruction autologous hamstring tendons grafts are currently a popular graft choice in addition to the gold standard, the autologous bone-patellar tendon-bone graft. When using a hamstring graft, the healing process between the tendon and bone takes longer to provide sufficient mechanical stability at the tendon-to-bone interface than does the bone-patellar tendon-bone [10, 23]. The incorporation of the tendon graft into surrounding bone often fails due to relative motion between the tendon and bone [9]. Histologically the incorporation consists of remodeling the trabecular bone around the tendon and newly formed collagen fibers that connect the tendon to bone. These collagen fibers (Sharpey's fibers) are oriented perpendicularly to the longitudinal axis of the tendon. Sharpey's fibers are perforating fibers between the periosteum and the underlying bone [2, 5, 21]. The tendon is attached to the periosteum, and the periosteum is anchored to the underlying bone through Sharpey's fibers (e.g., medial collateral ligament insertion on tibia).

The prolonged tendon-to-bone healing process does not allow early loading of soft tissue grafts compared to grafts that consist of bone-to-bone healing such as a bone-patellar tendon-bone graft [10]. Methods to enhance this healing process would contribute to earlier attainment of sufficient strength of graft fixation to allow early rehabilitation of the patients, and potentially improve the long-

term success of surgery following ACL reconstruction using hamstring tendons.

The administration of growth factors (e.g., transforming growth factor β and bone morphogenetic protein) at the time of surgery has been suggested to enhance the incorporation of soft tissue graft into bone tunnel [4, 24, 25, 32]. However, to date positive results are yet lacking in the literature. Rodeo et al. [18] have reported a histological and biomechanical analysis of tendon healing in a bone tunnel in a dog model. The results of this study indicate that healing occurs by bone ingrowth into the fibrovascular interface tissue that initially forms between the tendon and bone. There was progressive mineralization of the interface tissue, with subsequent bone ingrowth into the outer tendon and incorporation of the tendon graft into the surrounding bone. There was progressive reestablishment of collagen fiber continuity between the tendon and bone, resulting in reestablishment of a tendo-osseous junction. Biomechanical testing demonstrated a progressive increase in tendon pull-out strength that was correlated with the amount of bone ingrowth, mineralization, and maturation of the healing tissue.

Periosteum has osteogenic potential and has been used as a graft material for cartilage repair. It has been reported that periosteal cells produce a significant amount of type X collagen when cultured in vitro [27]. Type X collagen is a hypertrophic chondrocyte-specific collagen which plays an important role in mineralization of growth plate, fracture callus, and endochondral ossification of fracture repair [3, 8, 16, 17, 20, 28].

Therefore we hypothesized that periosteum can enhance the healing process of a tendon in a bone tunnel and lead to significantly better biomechanical fixation in a shorter period of time. This study evaluated the effect of periosteum on the tendon-to-bone healing using a rabbit model.

Materials and methods

The study was performed with 20 healthy, skeletally mature New Zealand white rabbits weighing 3–3.5 kg. Animal experimentation was carried out under the Role and Regulation of the Animal Care and Use Committee, School of Medicine, Kyungpook National University. The animals were anesthetized with 40 mg/kg intramuscular ketamine hydrochloride (Ketalar, Sigma, St Louis, Mo., USA) and 10 mg/kg xylazine (Rompun, Sigma). The long digital extensor tendon of the knee joint of both hind limbs was detached from its femoral insertion and was transplanted through a bone tunnel into the proximal tibial metaphysis. A periosteal patch (5× 5 mm) was harvested from the proximal tibia, wrapped around the proximal end of the long digital extensor tendon of one limb, and secured with a 5-0 monofilament Nylon suture at each end. At that time the inner cambium layer of the periosteum was placed "face-on" with the tendon side. The diameter of the tendon and length of the tunnel was measured. The periosteum-wrapped tendon was fixed through a 2.5-mm diameter hole made obliquely through the proximal tibial metaphysis. In order to fix the tendon graft into the tibia a Bunnell suture using 5-0 monofilament of Nylon was inserted in the distal end of the tendon, drawn through the tibial tunnel, and secured to soft tissue. The tendon's diameter was constant, and the tendon was snugly fitted into the bone tunnel. The tendon was in contact with bone throughout the length of the tunnel (Fig. 1). The joint capsule, fascia, subcutaneous tissues, and skin were closed with interrupted 3-0 Vicryl suture (Ethicon, Somerville, N.J., USA). At the contralateral leg the same procedure was performed without periosteal wrapping to serve as a control. The rabbit returned to the cage after surgery. No immobilization of the legs was performed postoperatively. Evaluation was performed by histological and biomechanical tests on the Instron machine (Instron 4200 series IX automated Material Testing system V4.25a, Instron, Canton, Mass., USA). The rabbits were killed 3 weeks (n=10) and 6 weeks (n=10) after surgery. In each group and time period eight of the ten specimens were used for biomechanical testing; the remaining two specimens were used for histological evaluation.

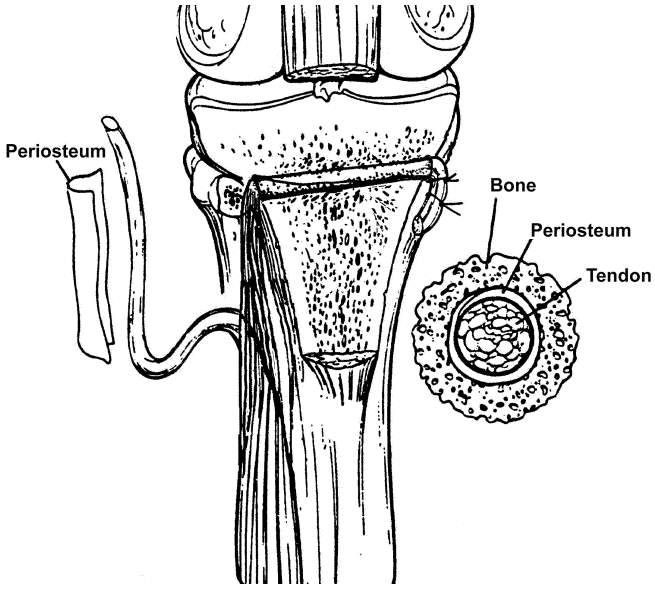

Fig. 1 The periosteum was wrapped around the tendon and the tendon was then transplanted into a drill hole in the proximal tibia

Histological study

Soft tissues were removed leaving only the tibia and transplanted tendon. The specimens were fixed in a 10% buffered formalin solution immediately after harvesting from each limb. After the specimens were decalcified, they were embedded in paraffin blocks. The specimens sectioned vertical to the longitudinal axis of the bone tunnel were stained with hematoxylin and eosin and Masson's trichrome stain. They were examined under light microscopy.

Biomechanical study

Each specimen for biomechanical testing was wrapped in gauze moistened with physiological saline solution and then wrapped in airtight polychlorovinylidene film. The specimens were stored at –32°C until the time of testing. Before the mechanical testing each knee was thawed overnight at 4°C. All soft tissues other than the graft were carefully dissected. The suture used for intraoperative fixation of the tendon was removed. A cyclic test with a low load

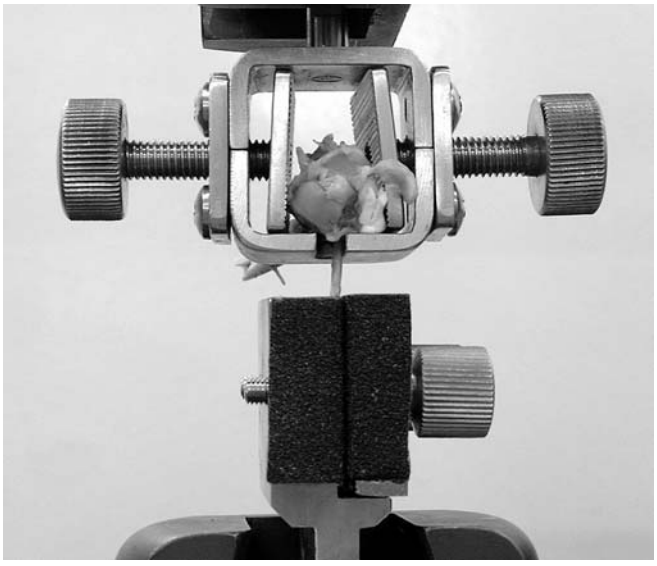

Fig. 2 The tibia was oriented for biomechanical testing such that the pullout loads were oriented in line with the bone tunnel

(5 N for ten times) was performed to determine stiffness of the bone-tendon interface at the tunnel entrance. Following this a load-to-failure test was performed. The tibia was clamped in a specially designed fixture. The muscle and the tendinous portion of the long digital extensor tendon were grasped in a pneumatic clamp, and the tibia was positioned to allow tensile loading aligned with the long axis of the bone tunnel (Fig. 2). The tendon was loaded on a material testing machine (Instron 4200 series IX automated Material Testing system V4.25a, Instron) at a rate of displacement of 50 mm/min until failure of fixation or the tendon ruptured at its midsubstance. The ultimate pullout load stiffness and the site of pullout were recorded. The failure mode was noted for each specimen. Since the length of the bone tunnel varied between specimens, the pullout load was normalized by dividing it by the length of the bone tunnel. The ultimate pullout load was considered the interface strength, and the normalized loads were designated the interference strength-to-length ratio.

A paired *t* test was used to determine statistical differences between the study groups after 3 and 6 weeks ($P<0.05$). One-way analysis of variance was used to compare the biomechanical data at different time points within each group ($P<0.05$).

Results

Histological findings

Three-week specimens

In the control specimens the interface between tendon and bone tunnel was filled fibrous tissue and was clearer and had no continuity. There was no cartilaginous component (Fig. 3A). In the periosteum-wrapped specimens examined at 3 weeks the space between the tendon and bony wall was filled with granulation tissue. Highly magnified observations showed that in granulation tissue perpendicular collagen fibers resembling Sharpey's fibers connected the tendon to the bony wall, and the interface was

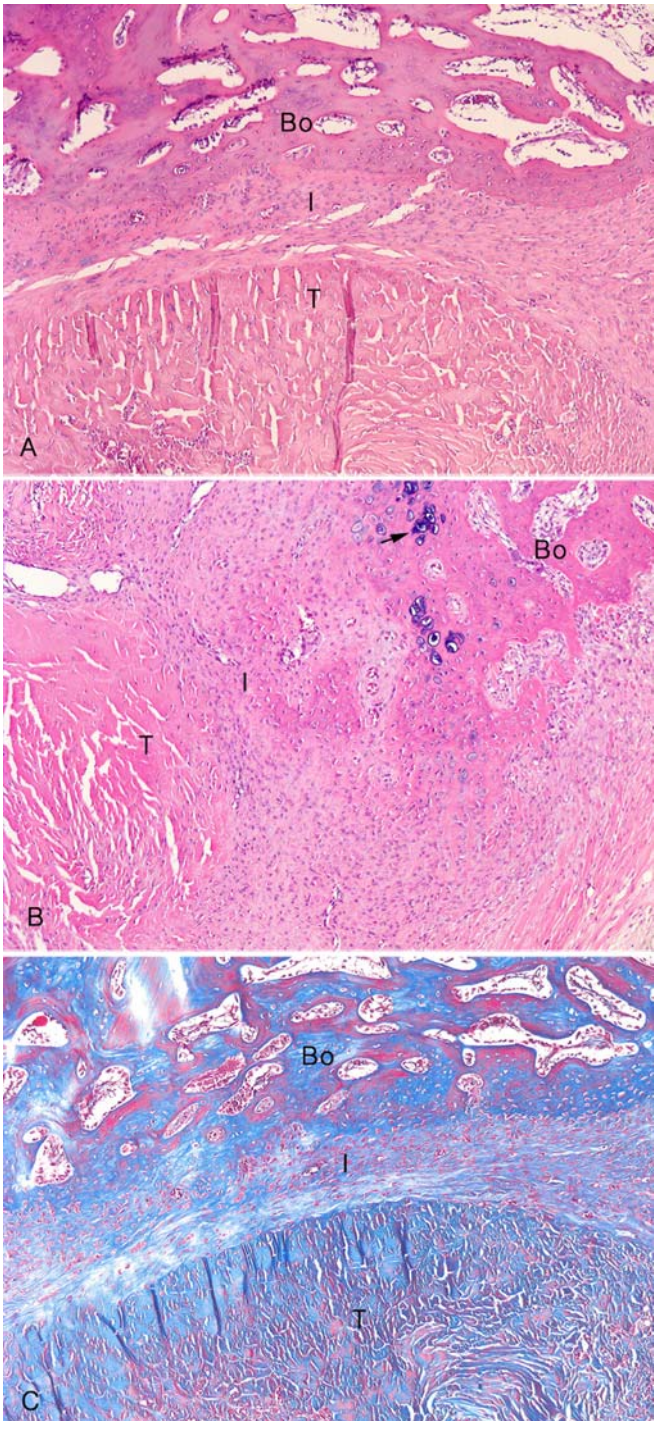

Fig. 3A–C Histological examination of 3-week specimen. *T* Tendon; *Bo* bone; *I* interface tissue between tendon and bone. **A** Specimen from control limb demonstrates that the interface was filled with fibrous tissue and was clearer and no continuity; hematoxylin and eosin stain, original magnification ×100. **B** Specimen from periosteum-wrapped limb demonstrates that an interface was filled with a granulation tissue with a highly cellular, fibrovascular tissue. Cartilaginous cells (*arrow*) were seen; hematoxylin and eosin stain, original magnification ×100. **C** Trichrome stain shows perpendicular collagen fibers connecting the tendon to the bone wall; Masson's trichrome stain, original magnification ×100

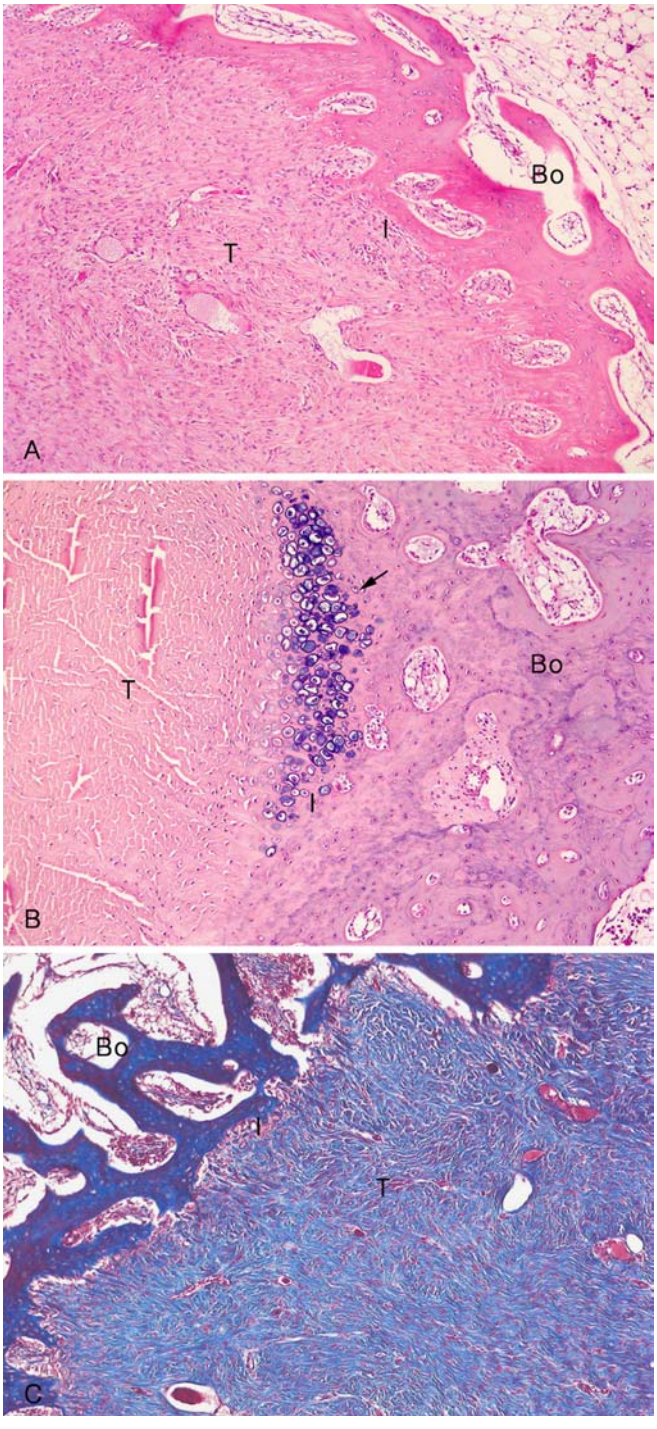

Fig. 4A–C Histological examination of 6-week specimen. *T* Tendon; *Bo* bone; *I* interface tissue between tendon and bone. **A** Specimen from the control limb demonstrates the interface was more matured than in the 3-week specimen, but there was no cartilaginous component and much less new bone formation; hematoxylin and eosin stain, original magnification ×100. **B** Specimen from periosteum-wrapped limb demonstrates an interface that was more obscure; the cartilaginous component was increased (*arrow*); hematoxylin and eosin stain, original magnification ×100. **C** Trichrome stain demonstrates perpendicular collagen fibers were seen crossing the tissue junction. There was increased collagen fiber continuity between the new bone and the tendon; Masson's trichrome stain, original magnification ×100

obscure. There was a highly cellular, fibrovascular interface tissue between the tendon and bone. Cartilaginous cells were also seen where the fibers were perforating the osteoid tissue. These cartilaginous cells were considered similar to cells found in normal bone-tendon junctions (Fig. 3B, C).

Six-week specimens

In the control specimens the interface was more matured than in the 3-week specimen, but there was no cartilaginous component and much less new bone formation. There was persistent fibrous interface tissue in the control group (Fig. 4A). In the periosteum-wrapped specimens the interface between the tendon and bone wall was more obscure, and the cartilaginous component was increased. Perpendicular collagen fibers resembling Sharpey's fibers were seen crossing the tissue junction. There was increased collagen fiber continuity between the new bone and the tendon (Fig. 4B, C).

Biomechanical testing

Failure mode

Three-week specimens. In the control groups four of eight specimens failed by tendon pullout from the bone tunnel and the remaining four failed outside the tunnel (Table 1). In the periosteum-wrapped groups three of eight specimens failed by tendon pull-out from the bone tunnel; the remaining five specimens failed by rupture in the midsubstance of the muscle or at the muscle tendon junction. The failure mode was very similar between the two groups.

Six-week specimens. In the control groups six of eight specimens failed by tendon pullout from the bone tunnel; the remaining two failed by outside the tunnel (Table 1). In the periosteum-wrapped groups two of eight specimens failed by tendon pullout from the bone tunnel; the remaining six failed by outside the tunnel. There were more tendons failed by outside in the periosteum-wrapped group than the control group.

Ultimate load to failure

The periosteum-wrapped limbs had a higher interface strength than the control limbs in both the 3-week (P=0.042) and the 6-week specimens (P=0.039). There was a significant increase in the interface strength of the 6-week specimens compared with the 3-week specimens for both the periosteum-wrapped limbs (P=0.004) and the control limbs (P=0.024; Fig. 5).

Table 1 Results of biomechanical testing in the periosteum-wrapped and control groups

	3 weeks (n=8)		6 weeks (n=8)	
	Periosteum	Control	Periosteum	Control
Site of tendon failure				
Tunnel	3	4	2	6
Outside	5	4	6	2
Ultimate load to failure (N/mm)	31.5±10.9*	21.6± 9.9	46.9±13.3**	32.7±13.3
Stiffness (N/mm)	35.6± 9.2	33.5±14.7	45.3±18.3	41.7±21.9

*P=0.042, **P=0.039

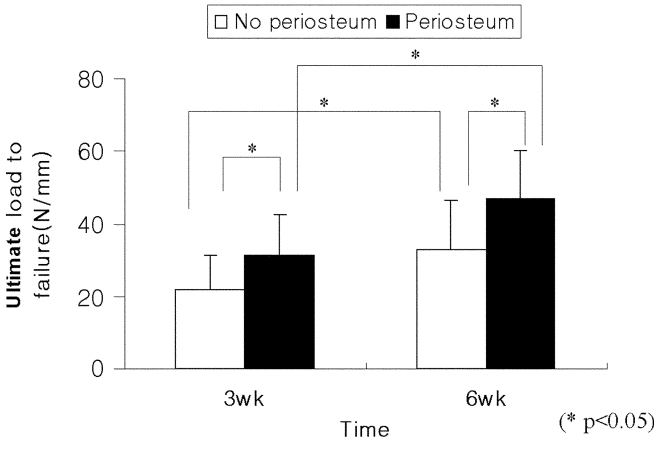

Fig. 5 Normalized values for interface strength demonstrate the periosteum-wrapped limbs have a higher value than the control limbs in both the 3-week and 6-week specimens

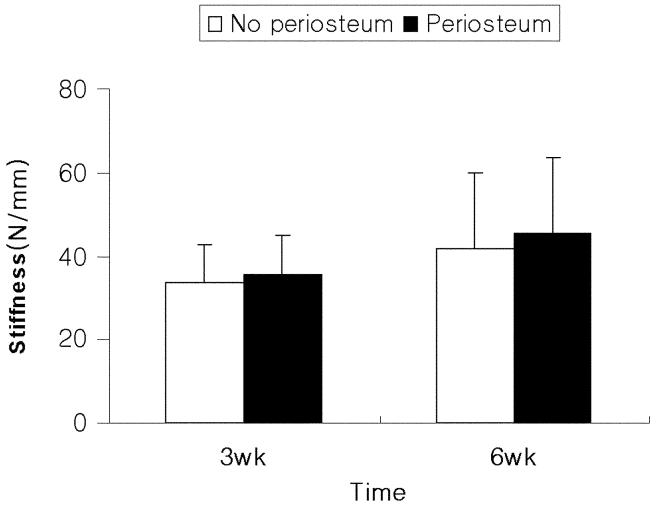

Fig. 6 There was no significant difference in the stiffness in each group

Stiffness

There were no significant differences in the stiffness between the periosteum-wrapped limbs and control limbs, or between the 3-week (P=0.30) and 6-week specimens (P=0.35) (Fig. 6).

Discussion

Since the site of tendon graft attachment to bone is the weak link in the early healing period, it is often necessary to delay weight bearing, range of motion, and specific activities to protect a healing graft from excessive loads [13]. The ability to accelerate healing between a tendon graft and bone may allow earlier return to functional activities and improve clinical outcomes. There are several reports on tendon-to-bone healing. However, there are few reports concerning enhancing tendon to bone healing using biological factors [6, 7, 12, 19, 22, 26, 33]. Rodeo et al. [19] reported that the biological factor bone morphogenetic protein 2 enhances tendon to bone tunnel healing. This study demonstrates that periosteum can accelerate the healing process when a tendon graft is transplanted into a bone tunnel.

Direct insertions contain four morphologically distinct phases in the transition from tendon to bone: tendon, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [1, 2, 5]. This direct insertion has been documented in the intact ACL and patellar tendon insertion zones [5, 11]. In contrast to direct insertions, distinct fibrocartilage transitional zones are characteristically absent in the indirect insertion [12, 21]. Indirect insertions consist primarily of superficial fibers, called Sharpey's fibers that insert into the periosteum at acute angles [31]. In the current study Sharpey's fibers were seen in the specimens obtained 6 weeks after surgery, further suggesting of an indirect insertion of tendon to bone [14, 21]. During growth Sharpey's fibers are thought to provide the structural matrix on which bone can advance with the progressive mineralization of ligament or periosteal collagen fibers [14]. Therefore it is possible that these fibers provide temporary support for the healing tendon to bone insertion, and with time these are remodeled.

Weiler et al. [29] studied the tendon-to-bone healing of the soft-tissue graft interference fit fixation in a model of ACL reconstruction in sheep. They reported two different mechanisms of tendon-to-bone healing: intratunnel and surface healing. A mature intratunnel tendon-bone junction with a zone of fibrocartilage was found after 9–12 weeks. At the tunnel entrance site a wide regular ligamentous insertion site was seen. This insertion showed regular patterns such as the direct type of insertion of a

normal ligament. Also Weiler et al. [30] reported a biomechanical study on tendon-to-bone healing. They found that the graft failed after 6 and 9 weeks mainly at the screw insertion site by intraligamentous rupture at the articular tunnel entrance. Direct interference fit fixation of a soft-tissue graft additionally alters the mechanical properties during its early remodeling. Our study model was an extra-articular rabbit model without interference screw fixation. Our current study showed the fibrocartilage at tendon-bone junction as early as 3 weeks in the periosteum-wrapped group, although partly.

Rodeo et al. [18] demonstrated that tendon-to-bone healing occurs by bone ingrowth into the fibrovascular interface tissue that forms between the edge of the bone tunnel and the tendon graft. Additionally, they recommended that a healing ligament be protected for at least 8 weeks after a reconstruction. Also, they reported that the strength of tendon-to-bone attachment increased until 12 weeks, at which time the bony attachment of the tendon was no longer the weakest link. Liu et al. [12] observed an indirect tendon to bone insertion site 6 weeks after surgery. Therefore the critical period of healing, at least in the rabbit model, has been identified as the first 6 weeks after surgery.

Park et al. [15] found that serial histological observations at the sites of tendon-to-bone healing show progressive restoration of collagen fiber continuity between bone and tendon. Perforating collagen fibers connecting tendon to bone appeared by 8 weeks. Another finding at the junction of the insertion of the tendon to bone was the formation of a layered structure of fibrocartilage by 12 weeks. While the Sharpey's perforating collagen fibers were seen within the intraosseous tunnel, the layered fibrocartilage was mainly around the entrance of the tendon into the tunnel. These findings may indicate a maturation of tendon-to-bone healing which can sustain a physiological load.

Our histological findings at 3 weeks did not show direct continuity between graft and tibia in control group, but exhibited more organization interface in the periosteum-wrapped group. Thus there was not adequate strength of fixation in either group at 3 week. In contrast, 6-week specimens of periosteum-wrapped group showed superior organization of the attachment of the graft to allow adequate mechanical strength than control group. Definite tendon-to-bone healing was noted in periosteum-wrapped group specimens while control group specimens showed only partial restoration of collagen fiber continuity between tendon and bone.

The higher biomechanical values in the periosteum-wrapped group than in the control group at 6 weeks were correlated well with the histological findings. It must be noted that the differences in attachment strength between the periosteum-wrapped group and control group were statistically significant at 3 and 6 weeks.

These histological and biomechanical results suggest that the healing of tendon to bone is mature in periosteum-wrapped tendon at 6 weeks, while the healing of tendon to bone is mature at 12 weeks without augmentation. These data suggest superior healing in periosteum-wrapped specimens. Since some failure occurred outside the tunnel in the periosteum-wrapped limb, the measured failure strength for these limbs was lower than the actual fixation strength. It can only be concluded that the fixation strength of the tendon in the tunnel is at least as high as the values measured.

Caution must be used when applying the results of this study to human patients. This model does not reproduce the complex biological and biomechanical environment of a tendon graft in an intra-articular bone tunnel. It is likely that the healing process in a rabbit occurs at a faster rate than in humans or dogs. These are important questions that need to be addressed before these findings can be applied to clinical situations.

This study suggests a potential of novel approach to the augmentation of the tendon-to-bone healing using a periosteal flap. Periosteum may be even more effective in situations in which there is excessive graft-tunnel motion, synovial fluid influx between the tendon and the bone, bone-tunnel flux between the tendon and the bone, or bone-tunnel widening. The results of this study may allow the eventual clinical application of periosteum in surgical reconstructions in which a tendon graft is transplanted into a bone tunnel. In addition to ACL reconstruction using semitendinosus and gracilis tendons, other potential applications include ulnar collateral ligament reconstruction in the elbow, lateral ankle ligament reconstruction, and rotator cuff tendon repair to the humerus. Further study is necessary in clinical intra-articular models to establish the effect of periosteum in tendon to bone tunnel healing.

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