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Effect of chitin on nonwoven fabric implant in tendon healing

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In 12 sheep (24 forelimbs), a 12 mm section of flexor digitorum superficialis tendon was removed. The tendons were repaired with (1) suture only (control group, $n = 8$), (2) suture plus implanted nonwoven polyester fiber (NWF group, $n = 8$), and (3) suture plus implanted nonwoven fiber and chitin complex (CP group, $n = 8$). All tendons were immobilized for 6 weeks. Macroscopic and histomorphometric evaluations were performed on two limbs from each treatment group in weeks 1, 3, 6, and 12. Macroscopic findings showed no significant differences among the three groups in any parameters. At the implant area, histomorphometry indicated that immature and intermediate fibroplasia was significantly greater in the CP group compared to the NWF group in week 1 and in weeks 3 and 6, respectively. In the area surrounding the implant, there were no significant differences among the three groups. © 1997 Elsevier Science Ltd

INTRODUCTION

Tendons and ligaments consist of parallel bundles of collagen fibers and have a different nutritional environment in comparison to other organs (Peacock, 1984), so their response to injury also differs. Various substances have been developed for use in tendon repair (Amadio, 1992). Carbon fiber has been used successfully to repair tendons in experimental and clinical studies involving many species (excepting the horse) (Bertone *et al.*, 1990), but this material does not accelerate wound healing.

Our previous studies have indicated that chitin accelerates the healing of skin and subcutaneous tissues by inducing angiogenesis and cell migration (Okamoto *et al.*, 1993a, b). In addition, chitin induces the production of several mediators, including prostaglandin E_2 (Minami *et al.*, 1995), interleukin-1, and fibroblast growth factor-like substances in dogs (Okamoto *et al.*, 1992), as well as interleukin-1 beta in humans (Tanigawa *et al.*, 1992). A complex of chitin and nonwoven polyester fiber was found to undergo organization in the flexor tendons of cows (Minami *et al.*, 1992a), and we recently observed that chitin induced type IV collagen and elastic fibers in bovine flexor tendon (Minami *et al.*, 1996). These results suggest that chitin may also accelerate wound healing in tendon tissue.

The objective of the present study was to evaluate the influence of chitin on the healing of sheep flexor tendons after repair with nonwoven polyester fiber.

MATERIALS AND METHODS

Animals

Twelve healthy adult female sheep were used in this study (Table 1). The flexor digitorum superficialis (FDS) tendon of both forelimbs were used in each animal. One of three tendon repair methods (eight limbs per method) was assigned in a balanced incomplete block design to compensate for differences between the sheep (Table 1).

Materials

Nonwoven polyester fabric (NWF: SN-1015H; Teijin Co., Tokyo) and a complex of chitin and NWF (Chitipack P™; Eisai Co., Tokyo) were supplied by Sunfive

Table 1. Experimental design

Sheep no.	POW[a] (weeks)	Assignment of forelimbs (X) to repair method		
		Control[b]	NWF[c]	CP[d]
1	1	X	X	
2		X		X
3			X	X
4	3	X	X	
5		X		X
6			X	X
7	6	X	X	
8		X		X
9			X	X
10	12	X	X	
11		X		X
12			X	X

[a]POW: Postoperative week.
[b]Suture only.
[c]Suture material was covered with nonwoven fiber.
[d]Suture material was covered with Chitipack P.

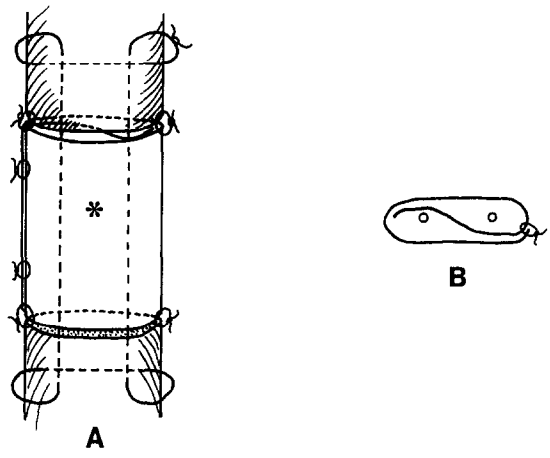

Fig. 1. Surgical procedure. (A) The tendon was sutured with a single locking loop suture using monofilament suture material, and 15 mm of separation was made between the end of tendon after suturing. Either NWF or Chitipack P (*) was placed in a modified figure-of-eight pattern to cover the suture material. (B) Transverse section of the implant area.

Co. (Tottori, Japan). Chitin was supplied by Nippon Suisan Co. (Tokyo, Japan), and was made of squid pen. Its characteristics were: ash, maximum 1%; protein content, maximum 0·3%; molecular weight, 370 000; heavy metals such as Pb, Cd and As, maximum 10 ppm. The manufacturing process of Chitipack P® has been described previously (Tanioka *et al.*, 1993). Monofilament polyglyconate (2-0 and 4-0; Maxon; Cynamid of Great Britain, Gosport, UK) was used for tendon suture and for attachment of the implant to the tendon ends, respectively.

Experimental design

Thiopentone (10 mg/kg) was administered for induction of anesthesia following intravenous administration of xylazine (0·1 mg/kg). Anesthesia was maintained with halothane and oxygen inhalation. Each sheep ($n = 3$) was placed in the supine position with the forelimbs suspended in extension and the metacarpal region of each forelimb was prepared for aseptic surgery.

A 50 mm straight skin incision was made over the palmar aspect of the middle of the metacarpal region. The subcutaneous tissue was dissected to expose the paratenon of FDS and the tendon was exposed following incision of the paratenon. A 12 mm deficit was created in the FDS tendon, centered over the middle of the tendon in the metacarpal region, using sharp dissection. The deficit was cut distal to the separation of FDS into deep and superficial heads. The tendon was first transected with a scalpel blade and then transected again after 12 mm was measured. Following retraction, an approximately 15 mm deficit remained in each tendon.

Each tendon was sutured with a single locking loop of 2-0 Maxon and the 15 mm gap was maintained between the cut ends after suturing. Either NWF or Chitipack P (15 mm × 15 mm) was implanted into this gap in two of the groups. The material was measured and cut with a scalpel blade, and then folded longitudinally into three equal parts that fitted the width of the tendon (approximately 5 mm). These implants were placed in a modified figure-of-eight pattern covering the suture material (Fig. 1). The implants were maintained in the folded position by two interrupted sutures of 4-0 Maxon and were held between the two tendon ends using four interrupted sutures of 4-0 Maxon. In the control group, tendon suture alone was performed.

The paratenon and subcutaneous tissues were closed separately with continuous 4-0 Maxon sutures and the skin incision was closed with a continuous 2-0 nylon suture. A fiberglass cast was applied to enclose the hoof and extended to just below the carpus. Each sheep was treated with preoperative antibiotics (procaine penicillin 20 000 IU/kg subcutaneously twice daily) and butorphanol (5 mg/kg intramuscularly once daily) for 3 days postoperatively. The animals were monitored daily to assess the degree of lameness and the condition of the cast. The casts were changed 6 weeks postoperatively, when the skin sutures were removed.

The same procedure was also performed at 6, 9, and 11 weeks after initial surgery in 3 sheep on each occasion. At 12 weeks after initial surgery, all sheeps ($n = 12$) were killed with intravenous pentobarbital (100 mg/kg). The samples harvested at 11, 9, 6, and 0 weeks after initial surgery were designated as being from postoperative weeks (POWs) 1, 3, 6, and 12, respectively (Table 1).

Macroscopic observation

After euthanasia, the FDS tendons were removed following palpation of the operative site through the

skin. Each tendon was evaluated macroscopically to determine the width and thickness of the proximal normal tendon, proximal cut end of the tendon, middle of the gap, distal cut end of the tendon, and distal normal tendon.

Microscopic observation

Specimens were fixed in 10% buffered formalin and embedded in paraffin following dehydration. Sections were cut longitudinally at 6 μm in thickness and were stained with hematoxylin and eosin. The sections were evaluated by the point-counting, line intercept technique using an SM Leitz microscope and Zeiss Integration-platte I grid at ×25 magnification (Norrdin *et al.*, 1977). The sites evaluated were the implant and the surrounding area. Twenty fields were observed in each area and parameters were expressed as a proportion of the total area (20 fields). Histologic features were defined as follows: granulation tissue consisted of fibroblasts oriented longitudinally with perpendicular vessels, hemorrhage, fibrin, and almost no collagen, while immature fibroplasia consisted of fibroblasts with large, round basophilic nuclei, and minimal collagen. Intermediate fibroplasia was divided into types A and B: type A consisted of fibroblasts with oval nuclei and longitudinal collagen with a pale pink color, while type B consisted of fibroblasts with more elongated nuclei and dense, longitudinal collagen with a dark pink color. Mature fibroplasia was normal tendon tissue composed of a few fibroblasts with extremely elongated nuclei and dense, thick longitudinal collagen fibers. The implant area showed very little type B intermediate fibroplasia and no mature fibroplasia. Therefore, type A and B intermediate fibroplasia were combined as intermediate fibroplasia. For evaluation of elastic fibers, the sections were also stained with Verhoeff van Giesen stain.

Statistical analysis

Analysis of variance was performed to compare differences among the repair methods for all parameters by Student's unpaired *t*-test using Visual Stat. Differences were considered significant at $p < 0.05$.

RESULTS

Macroscopic findings

In all sheep, the surgical wound healed completely. In the middle of the gap and at the proximal and distal cut ends of the tendon, both width and thickness gradually increased during the experimental period. There were no significant differences among the three groups at any time.

Microscopic findings

Table 2 shows the histomorphometric findings in the implant area. The area of filaments decreased in both groups. The percentage was >20% on POW 1, while it decreased to <15% on POW 12. Giant cells increased on POW 3 in both groups (Fig. 2); the percentage was significantly greater in the NWF group than in the CP group (17·0±0·6% and 7·4±0·6%, respectively). Immature fibroplasia was significantly greater in the CP group than in the NWF group on POW 1 (35·7±2·7% and 21·3±1·3, respectively) (Fig. 3). At other times, a similar trend was observed, but the difference was not significant. Intermediate fibroplasia was significantly greater in the CP group than in the NWF group on POWs 3 and 6 (Fig. 4). At other times, a similar trend was observed, but there was no significant difference. The area occupied by vessels also tended to be greater in the CP group than in the NWF group throughout the experimental period. On the other hand, the inflammatory cell area tended to be greater in the NWF group

Table 2. Histomorphometric findings of the implant area[a]

Week	Group	% Filament	% Giant cell	% Histiocyte	% Granulation tissue	% Immature fibroplasia	% Intermediate fibroplasia	% Vessel	% Inflammatory cell
1	NWF	24.3±2.7	0.4±0.3	5.6±2.0	4.6±1.4	21.3±1.3	0	1.3±0.4	2.5±0.7
	CP	22.7±0.4	0.3±0.4	7.1±0.7	3.5±3.8	35.7±2.7	0.2±0.3	2.0±0.8	1.4±0.3
		(p=0.493)	(p=0.8075)	(p=0.4192)	(p=0.7392)	(p=0.0207)	(p=0.4226)	(p=0.4063)	(p=0.1778)
3	NWF	15.9±0.7	17.0±0.6	16.8±3.4	0	31.9±9.8	1.6±1.4	1.2±0.0	0.6±0.8
	CP	16.0±0.3	7.4±0.6	10.2±6.2	0	44.8±6.8	9.0±1.7	3.7±1.0	0.6±0.0
		(p=0.8698)	(p=0.0035)	(p=0.3185)		(p=0.2646)	(p=0.0418)	(p=0.0702)	(p=1.00)
6	NWF	19.8±5.1	11.9±6.4	15.0±0.6	0	29.8±8.5	0.1±0.1	2.0±0.8	2.2±2.8
	CP	12.9±1.8	10.8±0.8	13.4±3.4	0	35.1±3.5	5.3±1.0	2.5±1.0	1.6±0.6
		(p=0.2132)	(p=0.8311)	(p=0.5784)		(p=0.5005)	(p=0.018)	(p=0.6419)	(p=0.7963)
12	NWF	14.3±1.5	10.7±1.0	12.9±6.9	0	42.3±6.4	1.5±0.7	2.4±0.8	0.9±1.0
	CP	14.8±0.3	14.5±4.1	5.7±0.4	0	43.0±1.4	6.5±3.3	5.2±2.3	0.1±0.1
		(p=0.6985)	(p=0.3308)	(p=0.2801)		(p=0.8932)	(p=0.1676)	(p=0.243)	(p=0.3753)

[a]Mean ± SD.

Fig. 2. POW 3 in the NWF group. Many giant cells (large arrows) were observed in the implant area. Small arrows indicate polyester fibers.

Fig. 3. POW 1 in the CP group. Space between polyester fibers (arrows) is occupied by immature fibroplasia, which consist of fibroblasts with large round basophilic nuclei and minimal collagen.

Fig. 4. POW 6 in the CP group. Many intermediate fibroplasia, which consist of fibroblasts with oval nuclei and longitudinal collagen, were observed in the space between polyester fibers (arrows).

than in the CP group throughout the experimental period. However, there was no significant difference of either parameter. Granulation tissue was only observed on POW 1 in both groups.

Table 3 shows the histomorphometric findings for the area surrounding the implant. Granulation tissue was only observed on POW 1. The area of this tissue was greater in the NWF and CP groups than in the control group and there was a significant difference between the control and CP groups. Granulation tissue occupied about 10% of the total surrounding area on POW 1, while immature fibroplasia occupied about 50% of the total surrounding area in all groups. Subsequently, the per cent granulation tissue area gradually decreased in all groups. On POW 6, granulation tissue only accounted for 0·8 to 2·1% of the total surrounding area. Type A intermediate fibroplasia was increased on POW 3 in all groups and accounted for $>50\%$ of the total surrounding area. The percentage of this tissue was significantly lower in CP group than in the other groups and it occupied about 50% of the total surrounding area on POWs 6 and 12. Type B intermediate fibroplasia was increased on POW 6 in all groups (Fig. 5). A few small areas of mature fibroplasia were also observed during the experimental period in all groups. Blood vessels occupied about 20% of the total surrounding area in all groups on POW 1 and decreased to $<10\%$ of the total surrounding area in all groups on POW 12.

Thin elastic fibers were only observed in the surrounding area in all groups, especially on POWs 1 and 3. These fibers gradually decreased. There was a tendency for them to be more prominent in the CP group than in the other groups.

DISCUSSION

The present study showed that chitin induced fibroplasia in nonwoven fabric (NWF) implants during the early phase of healing when buried in tendon tissue. It was also suggested that chitin induced maturation of collagen in NWF. The per cent area of blood vessels was greater in the CP group than in the NWF group during the experimental period. We have already investigated effects of chitin on NWF implants in canine subcutaneous tissue, and observed earlier organization of NWF as well as abundant angiogenesis in the presence of chitin (Okamoto *et al.*, 1993a). We also observed an increase of type IV collagen in the presence of chitin when NWF implants were buried in bovine tendon tissue (Minami *et al.*, 1996). Type IV collagen is mainly located in the basement membranes of blood vessels (Almedia *et al.*, 1992). The present results were consistent with these previous data.

Collagen is mainly produced by fibroblasts and its maturation occurs by continuous intermolecular and intramolecular cross-linking (Peacock, 1984). Its maturation is related to gravity or muscle contraction (Amadio, 1992). In the present experimental model, the implant itself did not directly receive muscle contraction force because the gap was maintained by suture mate-

Table 3. Histomorphometric findings of the surrounding area of the implant[a]

Week	Group	% Granulation tissue	% Immature collagen	% Intermediate A fibroplasia	% Intermediate B fibroplasia	% Mature fibroplasia	% Vessel	% Inflamatory cell	% Other cell
1	Control	2.5±0.0	47.0±13.6	17.7±9.8	7.9±0.4	0.3±0.4	23.7±3.2	1.0±0.1	0.0±0.0
	NWF	7.0±3.2	46.6±2.5	17.4±4.3	2.7±1.3	0.0±0.0	22.4±1.1	4.1±1.3	0.0±0.0
	CP	11.6±0.3	49.6±5.6	9.6±0.4	1.8±1.3	0.1±0.1	23.0±2.0	4.5±4.4	0.0±0.0
3	Control	0.0±0.0	15.9±5.8	65.9±3.6	4.7±2.5	0.0±0.0	11.2±1.9	2.5±2.2	0.0±0.0
	NWF	0.0±0.0	29.4±8.6	54.2±12.7	3.2±0.6	0.3±0.4	12.4±3.1	0.6±0.1	0.0±0.0
	CP	0.0±0.0	23.7±2.7	50.7±11.7	4.5±1.6	0.1±0.1	20.8±12.7	0.3±0.1	0.0±0.0
6	Control	0.0±0.0	0.8±1.1	43.1±7.1	31.5±11.2	1.2±1.1	18.5±2.9	10.6±14.0	1.8±0.3
	NWF	0.0±0.0	1.4±0.5	41.9±4.8	29.1±2.3	1.7±1.3	20.8±4.7	3.3±1.3	2.0±0.4
	CP	0.0±0.0	2.1±0.1	61.2±1.3	11.0±1.1	0.5±0.1	19.6±0.4	4.0±2.9	1.8±0.9
12	Control	0.0±0.0	0.2±0.3	46.7±34.5	37.5±29.2	0.0±0.0	9.9±2.5	3.1±2.5	2.7±0.0
	NWF	0.0±0.0	0.0±0.0	59.1±9.5	28.0±11.2	0.6±0.4	9.6±1.6	1.2±0.8	1.6±1.0
	CP	0.0±0.0	0.7±0.3	56.7±16.3	30.9±15.8	1.2±1.5	8.5±1.1	0.9±0.1	1.3±0.5

[a]Mean ± SD.

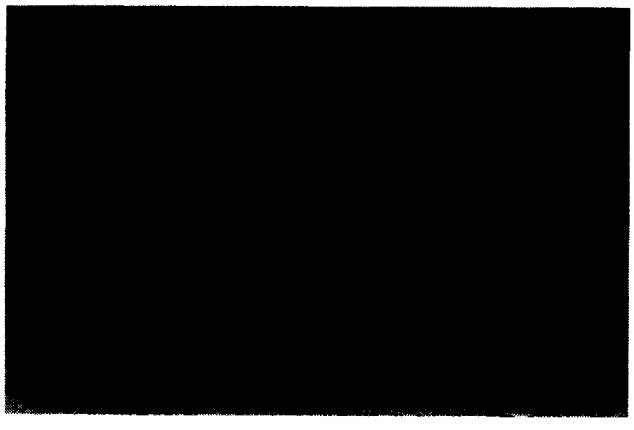

Fig. 5. POW 6 in the NWF group. Type B intermediate fibroplasia, which consist of fibroblasts with more elongated nuclei and dense longitudinal collagen, were observed in the surrounding area of the implant.

rial. Therefore, other factors appear to be related to collagen maturation. Several cytokines have been suggested to have a role in extracellular matrix formation, including collagen maturation (Quaglino *et al.*, 1990, 1991), and chitin can induce some cytokines, including interleukin-1 and fibroblast growth factor (Okamoto *et al.*, 1992). Our present findings suggest that chitin may induce cytokines that enhance collagen maturation in tendon tissue. In the future, it will be necessary to analyze the cytokines and types of collagen induced in the tissues by chitin using immunological and immunohistological techniques.

Tendon tissue consists of a few cellular components and a large amount of extracellular matrix, mainly collagen. Therefore, the wound healing process in this tissue differs from that of other tissues that have a greater blood supply. Repair of tendon occurs from the endtenon and synovial sheath when the repair site is not immobilized (Gelberman *et al.*, 1983). In the present study, the repair site was immobilized with a cast for 6 weeks after surgery and there were no definite microscopic differences among the three groups in the area surrounding the implant. This suggests that chitin in the implant did not affect the surrounding tissues.

Giant cells were significantly greater in the NWF group than in the CP group on POW 3, indicating that the foreign body reaction against polyester fiber was greater in the NWF group. Based on the present study, this finding could not be explained. One possible reason is that the peak foreign body reaction against polyester fibers occurred earlier in the CP group than in the NWF group. Another possibility is that the foreign body reaction against polyester fibers was suppressed in the presence of chitin. Since chitin is known to stimulate mononuclear cells, which develop into giant cells, in canine subcutaneous tissue (Okamoto *et al.*, 1993a), it is more likely that the peak foreign body reaction occurred earlier in the CP group than in the NWF group. However, there are no other data to support this hypothesis, so further investigation is necessary.

In conclusion, chitin may have a beneficial effect on collagen differentiation around NWF tendon implants. In this study, a biomechanical analysis including assessment of the tensile strength of the repaired tendons was not performed, so further investigation is necessary regarding this point.

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