0363-5465/88/1606-0616$02.00/0
THE AMERICAN JOURNAL OF SPORTS MEDICINE, Vol. 16, No. 6

Chronic Achilles paratenonitis

An immunohistologic study of fibronectin and fibrinogen

MARTTI H. KVIST*† MD, MATTI U. K. LEHTO,‡ MD, PhD, LASZLO JOZSA,§ MD, PhD, MARKKU JÄRVINEN,|| MD, PhD, AND HELMER T. KVIST,[a] MD, PhD

*From the *Paavo-Nurmi Center of Turku, Sports Medical Research Unit, Turku, Finland, ‡Department of Surgery, Turku University Central Hospital, Turku, Finland, §Department of Morphology, National Institute of Traumatology, Budapest, Hungary, ||Department of Surgery, Tampere University Central Hospital, Tampere, Finland, and the [a]Division of Surgery, District Hospital, Rauma, Finland*

ABSTRACT

Pathological alterations in chronic Achilles paratenonitis were studied histologically and using immunofluorescence techniques for fibronectin and fibrinogen in tissue samples obtained operatively from 11 athletes with this complaint and from 4 male cadavers serving as controls. The average duration of the paratenonitis was 20.4 months. The paratendineal fatty areolar tissue was clearly thickened and edematous, showing widespread fat necrosis and considerable connective tissue proliferation. The blood vessels were often obliterated and degenerated. Fibronectin and fibrinogen were commonly found in the proliferating connective tissue areas and in the vascular walls. Exudates rich in fibrinogen and fibronectin were seen in the inflamed paratendineal tissues, but not in the controls.

The results indicate that increased vascular permeability and fibrin formation still persist in chronic Achilles paratenonitis and that marked obliterative and degenerative alterations of the blood vessels are frequent. The presence of fibronectin and fibrinogen points to an immature nature of scar tissue in chronic paratenonitis.

Paratenonitis (peritendinitis) of the Achilles tendon is one of the most common overuse injuries seen in sports medicine clinics.[4,7,20] Compared to most other overuse injuries this complaint causes both competitive and recreational athletes to abandon their activities for a longer time and leads to a higher frequency of surgery.[21,41] Acute cases of Achilles paratenonitis are often accompanied by crepitation, due to the fibrin that is precipitated from fibrinogen-rich edematous fluid around the tendon.[33] In chronic cases, marked adhesion formation and often some nodes with marked tenderness are found around the Achilles tendon.[23]

Fibronectin is a ubiquitous high-molecular-weight glycoprotein which is involved in many biological processes.[10,15,32] Fibronectin has a marked affinity for both native and denatured collagen, fibrinogen and fibrin, glycosaminoglycans,

TABLE 1
Basic patient data

Case no.	M	F	Age (years)	Sports	Duration of symptoms
Patients					
1		x	20	High jumping	5 months
2	x		67	Jogging	6 months
3	x		23	Middle distance running	7 months
4	x		34	Long distance running	8 months
5		x	29	Orienteering	1 year
6	x		42	Various keep fit activities	1 year
7	x		45	Jogging	2 years
8	x		47	Jogging	2 years
9	x		35	Long distance running	2.5 years
10	x		42	Jogging, orienteering	3 years
11	x		26	Jogging	5 years
Controls					
12	x		32		
13	x		29		
14	x		21		
15	x		42		

† Address correspondence and reprint requests to: Martti Kvist, MD, Sports Medical Research Unit, University of Turku, Kiinamyllynk 10, SF-20520 Turku, Finland.

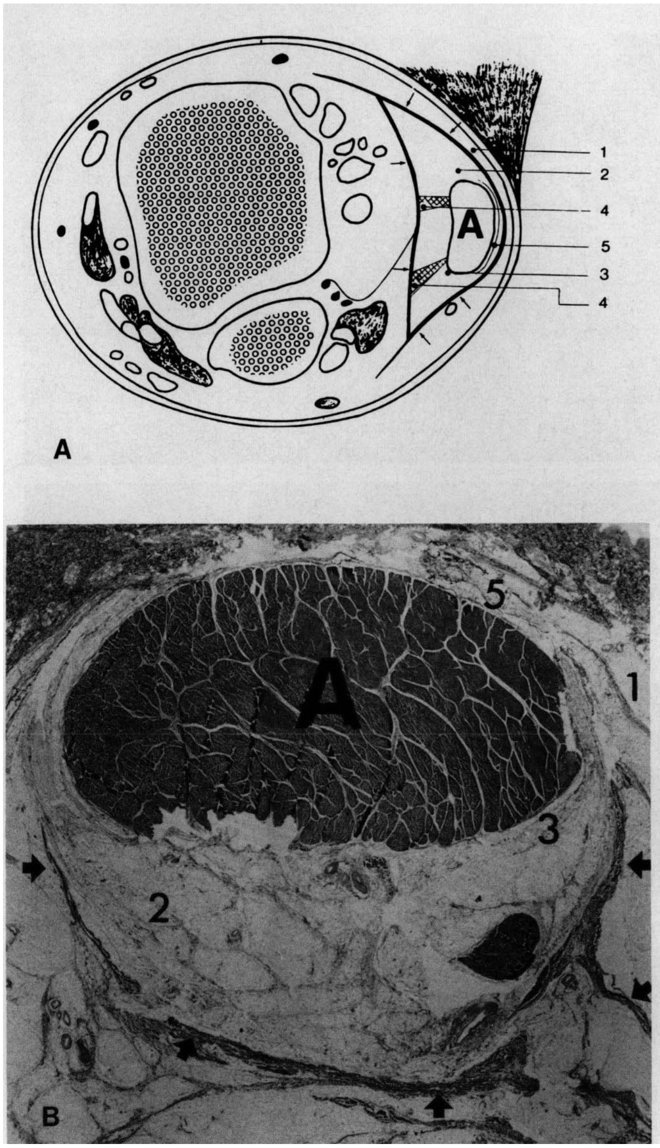

Figure 1. A, the Achilles tendon (A) is surrounded by the superficial and deep layers of the crural fascia (→). Numbers indicate biopsy sites. Biopsies were taken from: 1) the subcutaneous tissue; 2) the macroscopically thickened and edematous paratendineal tissue; 3) the ventral corner close to the tendon surface; 4) the adhesions in Kager's triangle; 5) the gliding membranes on the dorsal side (illustration modified from Lang and Wachsmuth[24]). B, transversal section (3.5 cm above the calcaneus) of normal Achilles tendon (A) and paratendineal tissues of a male victim of accidental death (age 32). Numbers indicate biopsy sites, which are explained in A. Plantaris tendon (P) and the crural fascia with its superficial and deep layers (➧) are demonstrated. Van Gieson ×6.5.

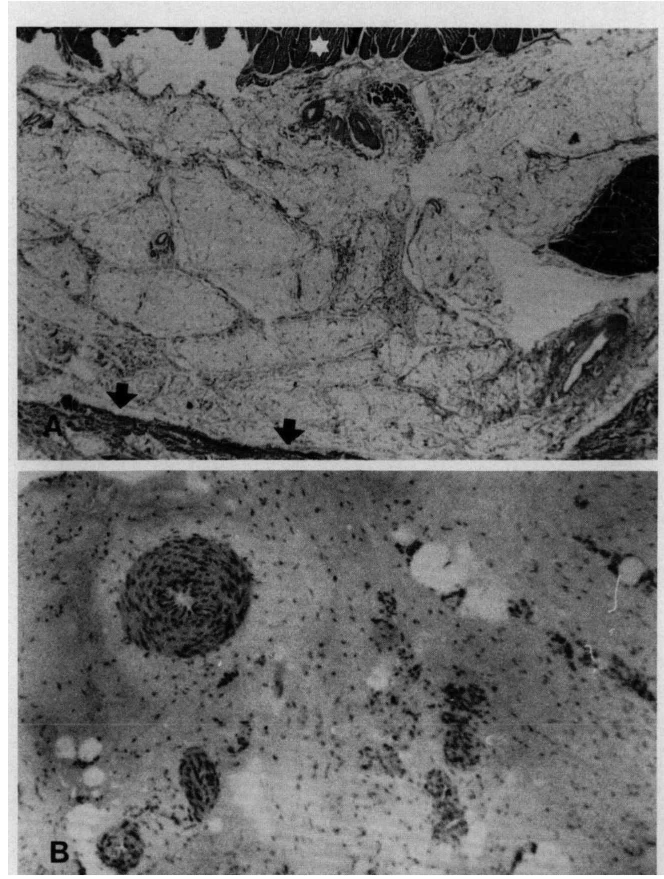

Figure 2. A, the normal paratendineal fatty areolar tissue of the Kager's triangle-space, filling ventrally the fascial compartment enclosing the Achilles tendon (★), is demonstrated. The deep layer of the crural fascia (➧) is seen. The biopsy was taken from the same subject as in Figure 1B. Van Gieson ×8. B, in the inflamed paratenon, loose connective tissue is seen with neoformation of small blood vessels. Obliteration of a muscular artery is seen. Van Gieson ×100.

Factor $XIII_a$, etc.[15] During tissue repair, fibronectin is initially codistributed with fibrin, forming a scaffold for migrating cells.[19] The adhesion of fibroblasts to fibrin is maximal if the fibronectin is cross-linked to the fibrin,[10] and this matrix promotes the organization of collagen.[11] The early abundant appearance of fibronectin in granulation tissue is followed by its slow decline and final disappearance in normal healing processes.[14,19,27]

The role of fibrin, formed by the conversion of fibrinogen to fibrin, in inflammatory lesions is not fully understood.[13,35] In the first phase of injury the fibrinogen-fibrin network forms a temporary connective tissue.[14] The constituents of fibrin and thrombin, Factor $XIII_a$ and fibronectin and their degradation products, have stimulatory effects on cellular ingrowth.[16,35] Fibrin is important but not necessary for the repair process.[13]

There are only a few histopathologic reports on Achilles tendon paratenonitis, mostly based on limited patient materials.[2,9,12] In an ultrastructural study we found an increased amount of ground substance, Type I and III collagen fibrils, and an increased number of elastic microfibrils in this condition. Myofibroblasts represented 19% of the noninflammatory cells studied.[22] Histochemically we found increased catabolism and decreased oxygenation in the in-

TABLE 2
Presence of obstructed vessels according to both fibronectin (FN) and fibrinogen (FG) immunofluorescence staining[a]

Case no.	Biopsy sites[b]				
	1	2	3	4[c]	5
	FN + FG	FN + FG	FN + FG	FN + FG	FN + FG
Patients					
1	+	+	−	−	+
2	+	−	++	+	−
3	−	−	+	+	+
4	+	+++	−	+	+
5	−	++	+	++	−
6	+	++	+	++	++
7	+	++	++	++	+
8	+	+++	+	+++	+
9	−	++	++	+	−
10	−	+	+	+	++
11	++	+	−	−	+
Controls					
12	−	+	−		±
13	−	−	−		−
14	−	−	−		−
15	−	−	±		+

[a] Grading of frequency of obstructed vessels is as follows: −, none; ±, fortuitous; +, some; ++, moderate; +++, high.
[b] Biopsy sites are shown in Figure 1.
[c] Adhesions (Biopsy Site 4) were not present in the controls.

flamed paratenon, and histologically a massive formation of connective tissue, fat necrosis, vascular proliferation, and marked vascular alterations.[21]

The purpose of this study was to examine, using immunofluorescence techniques, the role of fibronectin and fibrinogen in the inflammatory process of Achilles paratenonitis.

MATERIALS AND METHODS

The paratendineal tissue samples for the immunohistologic and histologic studies were excised intraoperatively from 11 patients (mean age, 37.3 years; range, 20 to 67 years) with Achilles paratenonitis. The tissue samples were taken from the selected parts of the inflamed paratenon (Fig. 1A), and corresponding control samples (Fig. 1B) were taken from four healthy male cadavers (ages 32, 29, 21, and 42 years) who had died traumatically. The autopsy was done in all cases within 1 day after death. Operations were carried out in Rauma District Hospital and in Tampere University Central Hospital, Finland. The basic data on the patients are presented in Table 1. Most of the operated cases were subchronic or chronic, with an average duration of symptoms of 20.4 months (range, 5 months to 5 years).

Immediately after excision, the tissue samples were frozen in isopenthane, cooled to −180°C in liquid nitrogen and stored at −70°C until processed further. Serial sections of 8μm thickness were cut on a cryostat and stained with antihuman fibronectin antibodies (kindly provided by Prof. A. Vaheri) and antihuman fibrinogen antibodies (Dakopatts A/S, Glostrup, Denmark), which also gives a specific reaction with fibrin in man (Dakopatts, personal communication). Unfixed sections were preincubated in phosphate buffered saline (PBS) at +4°C for 30 minutes and air dried.

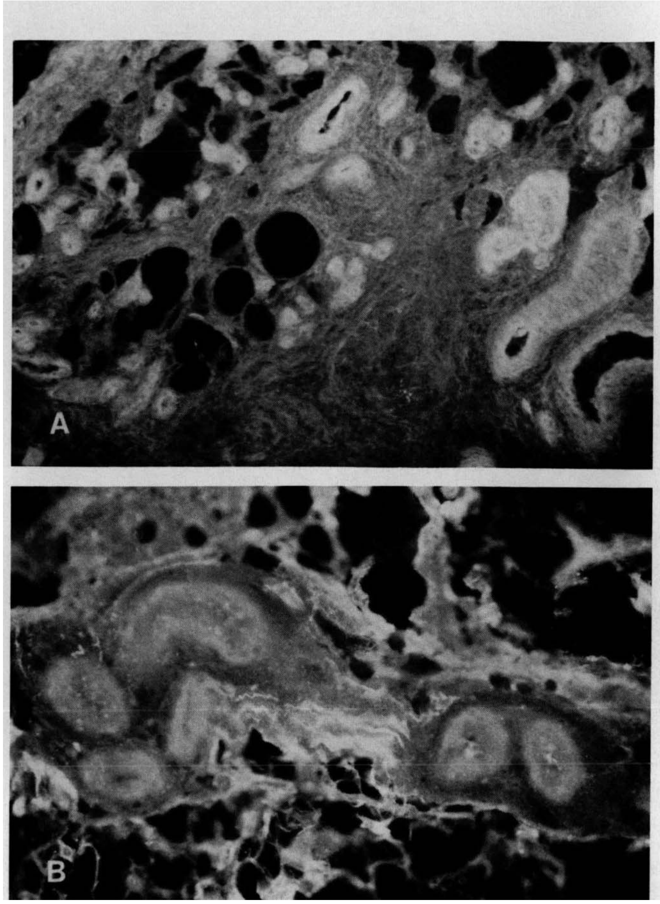

Figure 3. A, marked vascular proliferation is seen within the connective tissue of the inflamed paratenon (FN staining ×100), and B, blood vessels with profound degenerative changes are seen (FG staining ×100).

Then, 50 to 100 μl of primary antibody working dilution (1:100 for antifibronectin[26] and 1:50 for antifibrinogen) was pipetted on each section and incubated in a humid box at 22°C for 16 hours. The sections were washed three times with PBS, and air dried. Finally, incubation with fluorescein isotiocyanate (FITC)-conjugated antirabbit IgG (Wellcome Reagents, Ltd., U.K., dilution 1:20) was carried out for 30 minutes under conditions described above.

The concentrations of antibodies were kept constant throughout the whole series of experiments. Normal rabbit serum, PBS, and FITC conjugates alone were also tested in control stainings, in a similar manner.

The incubations were terminated by rinsing the sections three times with PBS. The specimens were mounted in glycerin jelly (Hopkin & Williams, U.K.). Epifluorescence photomicrography was performed with an Olympus microscope equipped with a camera unit.

For conventional histology the sections were stained with hematoxylin and eosin and van Gieson techniques.

RESULTS

Histologic findings

The subcutaneous biopsies (Biopsy Site 1) from the control subjects contained normal fat tissue with septae. The cor-

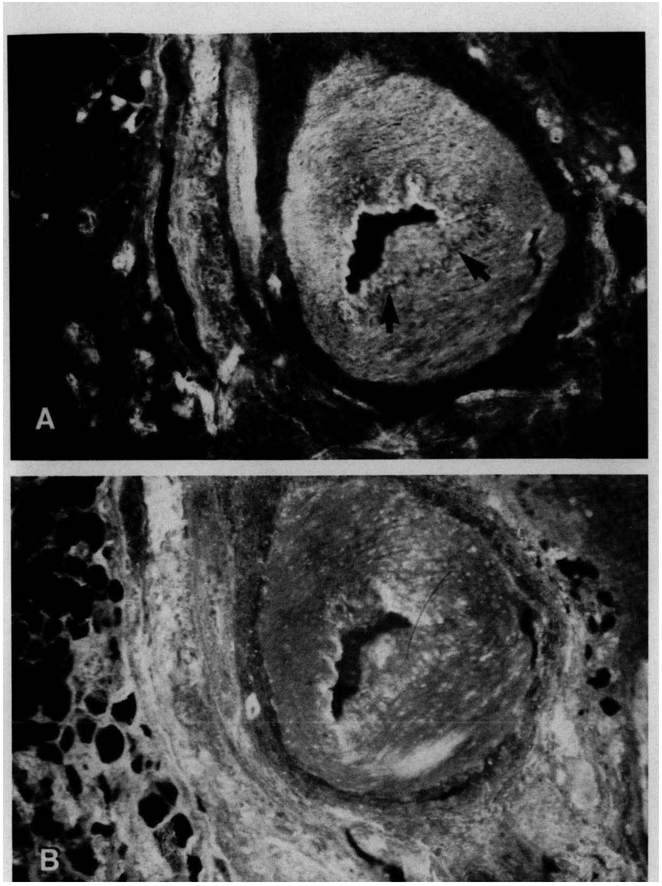

Figure 4. A, a fibrous plaque is seen within the intima (→) of a muscular artery in the inflamed paratenon. Moderate activity is seen in smooth muscle cells throughout the media. FN staining ×100. B, a faintly and diffusely stained fibrous plaque of an arteriosclerotic muscular artery (the same as in A) is seen. The surrounding connective and fat tissue exhibit moderate activity. FG staining ×100.

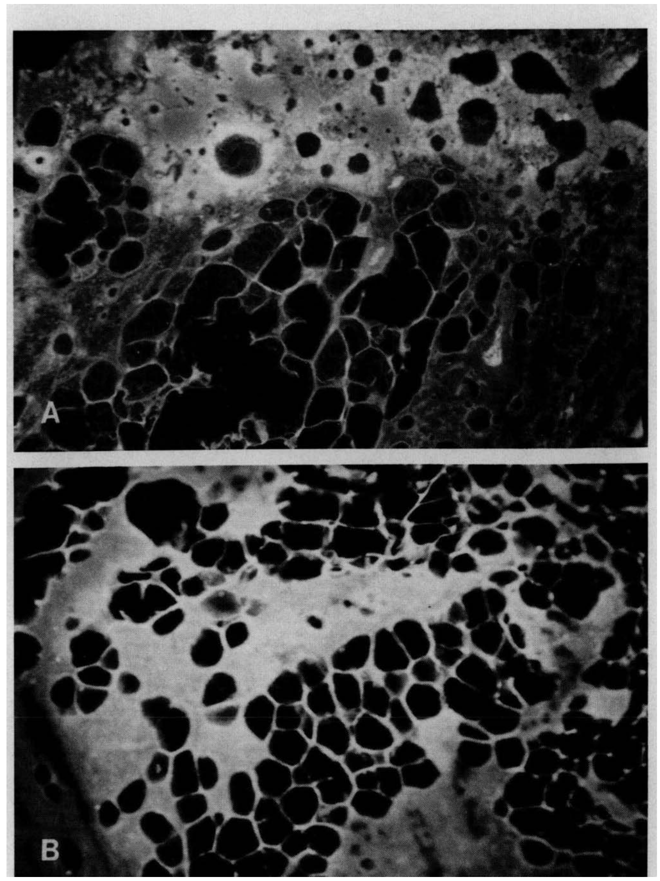

Figure 5. A, a profound fibronectin exudate is seen among the fat tissue of the inflamed paratenon. FN staining ×100. B, fibrinogen is seen as a homogeneous deposition within the fat tissue. FG straining ×100.

responding specimens from the cases of Achilles paratenonitis showed an increased deposition of connective tissue among the fat tissue.

In the control subjects, the paratendineal biopsies taken from the lateral, medial or ventral side of the tendon (Biopsy Site 2) contained normal loose areolar fatty tissue (Fig. 2A). In two control subjects we found evidence of some moderately obliterated arteries. The corresponding specimens from the cases of paratenonitis exhibited fibrinous exudations, widespread fat necrosis, marked neovascularization, degenerative vascular changes, and proliferation of loose connective tissue (Fig. 2B).

Adhesions (Biopsy Site 4) were not found in the control subjects; in the patients, however, adhesions were common.

The affected layer on the dorsal side of the tendon, a gliding membrane consisting of a number of truly thin gliding sheets (Biopsy Site 5), was hypertrophied, as was the paratendineal tissue on the ventral side close to the tendon (Biopsy Site 3). (The normal structure of a gliding membrane is presented in Figure 7B.) These inflamed paratendineal areas also showed vascular alterations (obliteration and neovascularization), as well as deposition of more mature connective tissue.

Immunohistologic findings

Both fibronectin and fibrinogen were abundantly distributed in the walls of the blood vessels of the affected paratenon. In the control subjects the walls of the arteries were in general less brightly stained. Some arteries of both control subjects and patients showed a staining reaction only in the intima of these vessels. In the patients, the capillary walls in general exhibited marked activity, whereas in the control subjects there was no or, more commonly, only slight activity.

Obliterative alterations in the blood vessels were frequently seen in all the affected paratendineal areas studied (Table 2).

Degenerative changes in the blood vessel walls were frequent in the inflamed paratenon, which locally exhibited profound vascular proliferation (Fig. 3). In some cases alterations resembling atherosclerotic changes were seen (Fig. 4). Areas of homogeneous deposition of both fibronectin and

TABLE 3
Presence of exudative deposits of fibronectin (FN) and fibrinogen (FG)[a]

Case no.	Biopsy sites[b] 1		2		3		4[c]		5	
	FN	FG	FN	FG	FN	FG	FN	FG	FN	FG
Patients										
1	+	−	±	±	++	+	+++	+	+++	+
2	+	−	+	±	++	+	−	−	±	±
3	−	−	+++	++	++	+	−	−	−	±
4	+	+	+	+	±	−	++	+	+++	++
5	±	−	−	−	−	−	+	±	−	−
6	−	−	+	+	+	−	−	−	++	+
7	±	+	−	−	−	−	−	−	±	±
8	−	−	+	+	+	±	+	±	+	+
9	−	−	+++	+++	++	+	−	−	−	+
10	−	−	+	+	−	−	−	−	++	++
11	−	−	+	±	+	±	+	−	±	−
Controls										
12	−	−	−	−	−	−			−	−
13	−	−	−	−	−	−			−	−
14	−	−	−	−	−	−			−	−
15	−	−	−	−	−	−			−	−

[a] See Table 2 for explanation of gradations.
[b] Biopsy sites are shown in Figure 1.
[c] Adhesions (Biopsy Site 4) were not present in the controls.

TABLE 4
Immunofluorescence intensity of fibronectin (FN) and fibrinogen (FG) in connective tissue[a]

Case no.	Biopsy sites[b] 1		2		3		4[c]		5	
	FN	FG	FN	FG	FN	FG	FN	FG	FN	FG
Patients										
1	+	++	++	+	++	+	++	+	++	+
2	+	+	±	±	+	+	+	±	±	±
3	+	+	+++	++	++	+	±	±	±	±
4	+	+	+	+	+	±	+	+	+	++
5	+	+	+	+	++	+	+	+	+	±
6	+	±	+	+	+	++	±	+	±	+
7	+	±	++	+	++	+	+	+	+	±
8	+	+	++	++	+	+	+++	++	++	+
9	±	±	++	++	++	+	±	±	++	+
10	+	+	++	++	+	±	+	±	±	±
11	++	+	++	+	++	++	+	+	+	+
Controls										
12	+	+	+	±	±	±			+	+
13	±	±	+	+	+	±			±	±
14	±	±	±	±	+	±			+	±
15	±	+	+	±	±	±			+	±

[a] Grading of fluorescence is as follows: ±, faintly positive; +, positive; ++, moderately positive; +++, conspicuously positive.
[b] Biopsy sites are shown in Figure 1.
[c] Adhesions (Biopsy Site 4) were not present in the controls.

fibrinogen were frequently seen in the inflamed paratenon (Fig. 5) due to the extravasation of these plasma proteins (Table 3). This was especially seen in paratendineal Biopsies 2 and 5 (Table 3). These exudates were most typically located in relatively small areas among the fat cells. A corresponding leakage was not found in the control subjects.

Slight activity was found in the control subjects for both fibronectin and fibrinogen mainly in the connective tissue septal areas (Fig. 6A). In the patients with paratenonitis, a clear increase in connective tissue formation was commonly found. The immunofluorescence staining reactions were quite varied for both fibronectin and fibrinogen in the connective tissue areas (Table 4). Compared to the controls, the connective tissue areas in general showed increased immunofluorescence staining reactions (Fig. 6B). The greatest activities were seen in the adhesions (Biopsy Site 4) and in the edematous paratenon obtained from both sides of the Achilles tendon. In the biopsies taken from the ventral side of the Achilles tendon (Biopsy Site 3) or from the gliding membrane (Biopsy Site 5), the immunofluorescence activity for fibronectin and fibrinogen was often slight or absent. The gliding membrane, especially, usually showed only slight activity, but moderate activity was seen in the surface areas (Fig. 7A), compared to the normal activity and structure seen in the controls (Fig. 7B).

In the patients, the fat cells were outlined by fibronectin and fibrinogen fluorescence of varying intensity that was stronger compared to the controls. The fat tissue of the inflamed paratenon was mostly replaced by new connective tissue, but small clusters of fat cells or fat cysts were still commonly seen amidst the connective tissue.

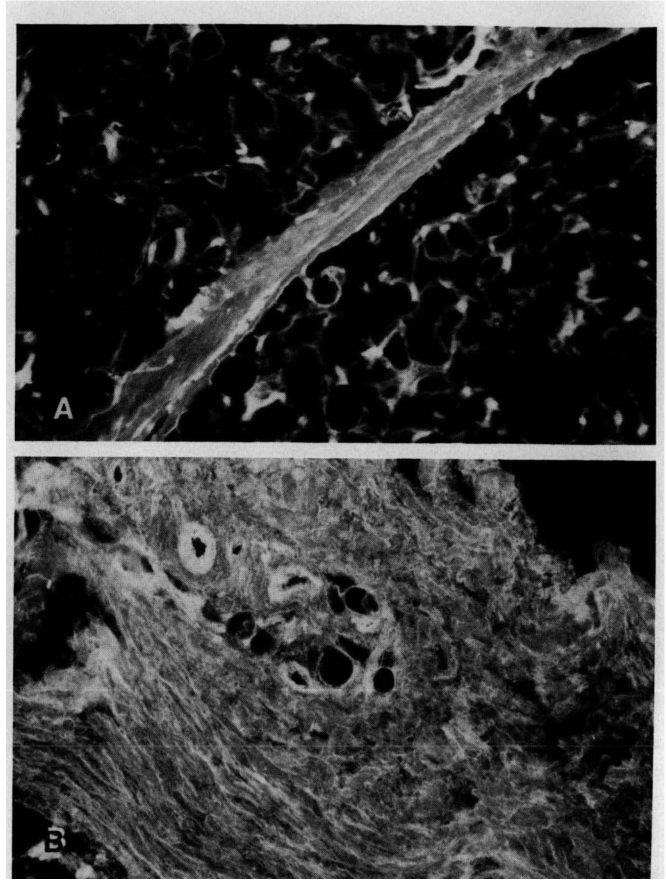

Figure 6. A, in normal areolar fatty tissue the activity is concentrated mainly in a septal area. FN staining ×100. B, a moderate activity is seen within the inflamed paratendineal connective tissue. FG staining ×100.

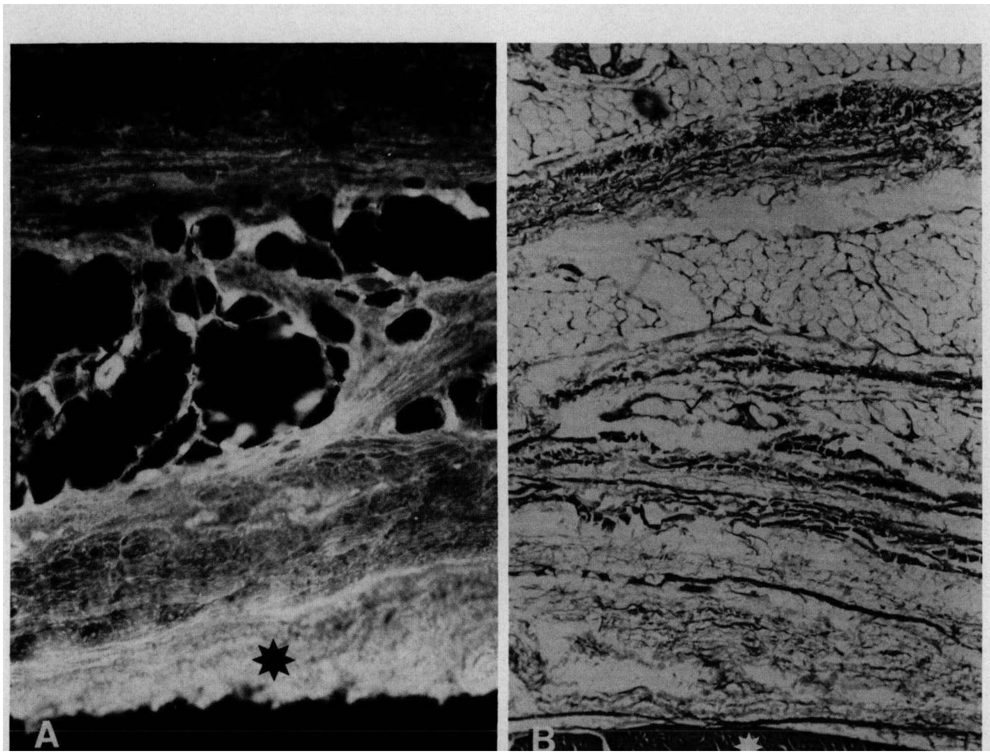

Figure 7. A, the surface area (*) of a hypertrophied and scarred gliding membrane exhibits marked activity. FN staining ×150. B, the structure of normal loose gliding membrane with fat cells and some thin gossamer-like sheets is seen adjacent to the Achilles tendon (*). The biopsy was taken from the same subject as in Figure 1B. Van Gieson ×50.

DISCUSSION

Fibronectin is normally found in loose connective tissue but not in dense mature connective tissue,[32,36] and it is distributed along the immature collagen fibers.[11,27,32] In soluble form it is present in plasma and other body fluids and in insoluble form in many tissues. Fibronectin can be synthesized, e.g., by fibroblasts and endothelial cells.[40] If the granulation tissue reaction persists, high levels of fibronectin and Type III collagen can be found.[10,19] These substances have a consistent codistribution.[10] Fibronectin appears to have many important effects throughout the tissue healing process[11] and it seems to be an early marker for connective tissue formation in pathologic lesions.[32,40] Fibronectin binds strongly and specifically to denatured collagen,[17] but interaction between fibronectin and native collagen is not well understood.[26]

A major finding in this study was that recognizable amounts of fibronectin and fibrinogen are still distributed in the chronically inflamed paratenon. This may imply a failure in the maturation of scar tissue in this complaint. An increased amount of fibronectin and fibrinogen was often found in the subcutis with paratenonitis, indicating affection of the subcutaneous tissue.

The membranes of individual fat cells may normally exhibit activity for fibronectin.[36] In this study fibronectin was found only faintly in the membranes of these cells in the control subjects, but both fibronectin and fibrinogen were often seen clearly in many paratendineal biopsies from the patients, suggesting that the fat cells are often affected in this disease.

Fibronectin can be produced in situ in the walls of blood vessels[3] and it is said to be a major component of atherosclerotic lesions.[37] In muscular arteries fibronectin is found in the pericellular matrix of the smooth muscle cells of the media, and in nonmuscular arteries the media contains thin strands of fibronectin.[36] Fibrinogen can be also found in moderation as linear or granular deposits in the vascular walls, but not on the stromal structures.[32] The increased angiogenesis commonly seen in this study is apparently due to the tissue hypoxia[18] of the affected paratenon.[21] The increased amounts of fibronectin and fibrinogen seen in many capillaries of the inflamed paratenon reflect endothelial proliferation.[3] These substances were seen abundantly in many arterial walls, indicating arterial wall damage.

Fibrin is formed by the conversion of fibrinogen to fibrin. Upon this conversion, fibronectin is incorporated into the fibrin network with the help of Factor $XIII_a$.[11] The presence of fibronectin and fibrinogen in the most inflamed paratendineal biopsies thus indicates the presence of fibrin as well, which has long been recognized as a hallmark of inflammatory responses.[34]

The fibrinogen antigenic material may also consist of fibrinogen-fibrin degradation products[6] and fibrinogen exudates are a sensitive measure of an altered vascular permeability.[5]

Some fibrinogen-fibrin derived degradation products may

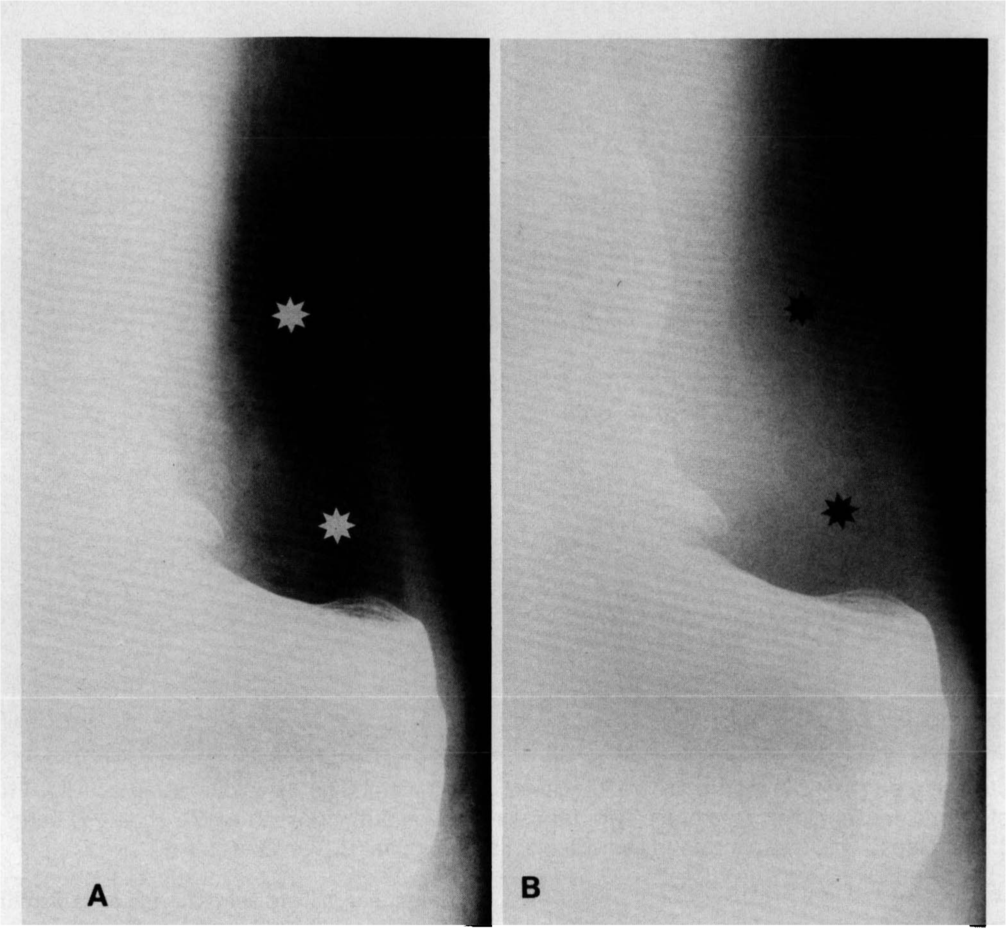

Figure 8. A, in soft tissue roentgenogram the normal Kager's triangle (*) is seen as a dark space. B, in acute paratenonitis soft tissue roentgenogram demonstrates a diffuse shadowing of Kager's triangle (*) (a picture taken 1 year earlier of the same patient as in A).

act as direct mediators of inflammation[34,35] and induce endothelial cell injury.[34] The fibrin endothelial cell interactions that occur may be extremely important in inducing vascular permeability changes and edema.[8,28,34,35] It has been reported that an accumulation of fibrin due to the inhibition of fibrinolysis can cause pulmonary microvascular injury.[31] According to these findings we postulate that fibrinogen-fibrin and their degradation products may play an important role in pathophysiology of Achilles paratenonitis, e.g., in the development of the vascular lesions found frequently in the present study. Furthermore, we posit that these alterations are possibly connected with some other mechanisms of the inflammation that increase vascular permeability[30] and pressure, with subsequent edema and pressure.

In acute Achilles paratenonitis a marked macroscopical swelling is often seen diffusely around the tendon. This can also be seen in soft-tissue roentgenograms as a diffuse shadowing of Kager's triangle (Fig. 8, unpublished data) apparently due to the marked extravasation of plasma proteins, including fibronectin and fibrinogen. We suggest that this extravasation can in many cases even in an early phase of paratenonitis lead to obvious vascular changes, with a continuing minor leakage of plasma proteins, and furthermore, to new vascular lesions. In addition, in many cases repetitive minor inflammatory reactions with extravasation of these plasma proteins apparently lead in time to vascular changes and the persistent leakage of fibronectin and fibrinogen commonly found in the inflamed paratenon (Table 3).

The findings from the present study indicate that in chronic or subchronic cases of Achilles paratenonitis distinct amounts of fibrin still exist in the affected tissues. Together with tissue hypoxia, this apparently constitutes the main reason for the marked adhesion formation in the disease.[1,21,23] The assignment of a central pathophysiologic role to the fibrinogen-fibrin complexes and their degradation products is supported by the facts that in peritendinitis crepitans systemic fibrinolytic treatment with heparin has proved to be very effective[33] and that local glycosaminoglycan polysulphate (GAGPS) injections can be beneficial in chronic cases of Achilles paratenonitis.[38] The GAGPS treatment has many heparin-like effects[29,39] and its suppression of the fibroblast proliferation and fibrosis in wound healing[25] is apparently due to fibrinolytic effects.[16]

The present results indicate that marked neovascularization and obliterative and degenerative changes exist in the capillaries, arterioles, and arteries in the inflamed paratenon of the Achilles tendon, apparently due to the different mechanisms of inflammation. Furthermore, the present results indicate that increased vascular permeability and fibrin formation still persist in chronic Achilles paratenonitis. This, together with the distinct amount of fibronectin in the inflamed paratendineal tissues, points to the immature nature of the scar tissue in chronic paratenonitis.

ACKNOWLEDGMENTS

Financial support from the Research Council for Physical Education and Sport, Ministry of Education, Finland, and the technical assistance of Mrs. Toini Vieno are gratefully acknowledged.

REFERENCES

1. Burleson RL, Ennulat N: Fibrin adherence to biologic tissues. *J Surg Res 25:* 523-529, 1978
2. Clancy WG, Neidhart D, Brand RL: Achilles tendonitis in runners—a report of five cases. *Am J Sports Med 4:* 46-57, 1976
3. Clark RAF, Quinn JH, Winn HJ, et al: Fibronectin is produced by blood vessels in response to injury. *J Exp Med 156:* 646-651, 1982
4. Clement DB, Taunton JE, Smart GW, et al: A survey of overuse running injuries. *Physician Sportsmed 9(5):* 47-58, 1981
5. Colvin RB, Johnson RA, Mihm MC, et al: Role of the clotting system in cell mediated hypersensitivity. I. Fibrin deposition in skin reaction in man. *J Exp Med 138:* 686-698, 1973
6. Danneskiold-Samsøe B, Clemmensen I, Andersen RB: The extra-articular deposition of fibrinogen antigenic material in patients with rheumatoid arthritis. *Scand J Rheumatol 8:* 87-90, 1979
7. Devereaux MD, Lachmann SM: Athletes attending a sports injury clinic—a review. *Br J Sports Med 17:* 137-142, 1983
8. Gerdin B, Saldeen T: Effect of fibrin degradation products on microvascular permeability. *Thromb Res 13:* 995-1006, 1978
9. Gould N, Korson R: Stenosing tenosynovitis of the pseudosheath of the tendo Achilles. *Foot Ankle 1:* 179-187, 1980
10. Grinnell F: Fibronectin and wound healing. *J Cell Biochem 26:* 107-116, 1984
11. Grinnell F, Billingham RE, Burgess L: Distribution of fibronectin during wound healing in vivo. *J Invest Dermatol 76:* 181-189, 1981
12. Harms J, Biehl G, Hochbach G: Pathologie der Paratenonitis achillea bei Hochleistungssportlern II. *Arch Orthop Unfall-Chir 88:* 65-74, 1977
13. Hedelin H, Lundholm K, Teger-Nilsson A-C, et al: Influence of local fibrin deposition on granulation tissue formation. *Eur Surg Res 15:* 312-316, 1983
14. Hlund B, Clemmensen I, Junker P, et al: Fibronectin in experimental granulation tissue. *Acta Pathol Mircobiol Immunol Scand(A) 90:* 159-165, 1982
15. Hynes RO, Yamada KM: Fibronectins: Multifunctional modular glycoproteins. *J Cell Biol 95:* 369-377, 1977
16. Kittlick PD: Fibrin in fibroblast cultures—a metabolic study as a contribution to inflammation and tissue repair. *Exp Pathol 17:* 312-326, 1979
17. Kleinman HK, McGoodwin EB: Localization of the cell attachment region in types I and II collagens. *Biochem Biophys Res Commun 72:* 426-432, 1976
18. Knighton DR, Silver IA, Hunt TK: Regulation of wound healing and angiogenesis—effect of oxygen gradients and inspired oxygen concentration. *Surgery 90:* 262-270, 1981
19. Kurkinen M, Vaheri A, Roberts PJ, et al: Sequential appearance of fibronectin and collagen in experimental granulation tissue. *Lab Invest 43:* 47-51, 1980
20. Kvist M, Järvinen M: Zur Epidemiologie von Sportverletzungen und Fehlbelastungsfolgen. Patienten-Analyse einer sportmedizinischen Poliklinik. *Med u Sport 20:* 375-378, 1980
21. Kvist M, Jozsa L, Järvinen M, et al: Chronic Achilles paratenonitis in athletes. A histological and histochemical study. *J Pathol 19:* 1-11, 1987
22. Kvist M, Jozsa L, Järvinen M, et al: Fine structural alterations in chronic achilles paratenonitis in athletes. *Pathol Res Pract 180:* 416-423, 1985
23. Kvist H, Kvist M: The operative treatment of chronic calcaneal paratenonitis. *J Bone Joint Surg 62B:* 353-357, 1980
24. Lang J, Wachsmuth J: *Praktische Anatomie, 1. Band, 4. Teil: Bein und Statik.* 2. Auflage. Berlin, Springer-Verlag, 1972, p 347
25. Larsson B, Fianu S, Jonasson A, et al: Mucopolysaccharide polysulphate reduces the fibrosis in healing abdominal surgical scars. A preliminary clinical and experimental evaluation. 2nd World Conference on Inflammation, Monte Carlo. Geneva, Bioscience Ediprint-Inc., Abstract A 199, 1986
26. Lehto M: Collagen and fibronectin in a healing skeletal muscle injury. An experimental study in rats under variable states of physical activity. *Ann Univ Turkuensis,* Ser D, University of Turku, 1983
27. Lehto M, Duance V, Restall D: Collagen and fibronectin in healing skeletal muscle injury. *J Bone Joint Surg 67B:* 820-828, 1985
28. Luterman A, Manwaring D, Curreri PW: The role of fibrinogen degradation products in the pathogenesis of the respiratory distress syndrome. *Surgery 82:* 703-709, 1977
29. MacGregor JR: Stimulation of urokinase activity by a polysulphated glycosaminoglycan present in Hirudoid®. *JRCS Med Sci 14:* 687-688, 1986
30. Majno G, Palade GE: Studies on inflammation, I—the effect of histamine and serotonins on vascular permeability; an electron microscopic study. *J Biophys Biochem Cytol 11:* 571-605, 1961
31. Malik AB, Johnson A, Tahamont MV: Mechanisms of lung vascular injury after intravascular coagulation. *Ann NY Acad Sci 384:* 213-234, 1982
32. Nagata H, Ueki H, Moriguchi T: Fibronectin. Localization in normal human skin, granulation tissue, hypertrophic scar, mature scar, progressive systemic sclerotic skin and other fibrosing dermatoses*Arch Dermatol 121:* 995-999, 1985
33. Rais O: Heparin treatment of peritenomyosis (peritendinitis) crepitans acuta. *Acta Chir Scand Suppl 268:* 1961
34. Rowland FN, Donovan MJ, Picciano PT, et al: Fibrin-mediated vascular injury. Identification of fibrin peptides that mediate endothelial cell retraction. *Am J Pathol 117:* 418-428, 1984
35. Senior RM, Skogen WF, Griffin GL, et al: Effects of fibrinogen derivatives upon the inflammatory response. *J Clin Invest 77:* 1014-1019, 1986
36. Stenman S, Vaheri A: Distribution of a major connective tissue protein, fibronectin, in normal human tissues. *J Exp Med 147:* 1054-1064, 1978
37. Stenman S, von Smitten K, Vaheri A: Fibronectin and atherosclerosis. *Acta Med Scand Suppl 642:* 165-170, 1980
38. Sundqvist H, Forsskåhl B, Kvist M: A promising novel therapy for achilles peritendinitis: double-blind comparison of glycosaminoglycan polysulfate and high-dose indomethacin. *Int J Sports Med 8:* 298-303, 1987
39. Törngren S, Kettunen K, Lahtinen J, et al: A randomized study of a semisynthetic heparin analogue and heparin in prophylaxis of deep vein thrombosis. *Br J Surg 71:* 817-820, 1984
40. Vaheri A, Salonen E-M, Vartio T, et al: Fibronectin and tissue injury, in Woolf N (ed): *Biology and Pathology of the Vessel Wall.* Eastbourne, England, Praeger, 1983, pp 161-171
41. Williams JGP: Achilles tendon lesions in sport. *Sports Med 3:* 114-135, 1986