THE EFFECT OF INJECTION OF HYDROCORTISONE INTO RABBIT CALCANEAL TENDONS

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Spontaneous rupture of tendons has been reported in patients receiving either systemic or local steroid therapy. In most cases the patients were receiving systemic steroid therapy for rheumatoid arthritis, systemic lupus erythematosus or polyarteritis nodosa (Cowan and Alexander 1961, Lee 1961, Smaill 1961, Melmed 1965). Most of the tendon ruptures after local steroid infiltration occurred after muscular activity (Lee 1957; Ismail, Balakrishnan and Rajakumar 1969; Bedi and Ellis 1970). It seems certain that hydrocortisone plays at least some part in the tendon rupture (Sweetnam 1969) but there is no direct evidence to support this. The present study was undertaken to find out whether infiltration of steroid into the tendons of rabbits produces any damage to the tendons which may contribute to their rupture.

MATERIALS AND METHODS

Thirty-one adult white rabbits, each weighing between two and three kilograms, were used. They were anaesthetised with open ether. The skin on the back of each hind limb was shaved from the level of the knee to the calcaneus. The tendo calcaneus was made taut by dorsiflexing the foot. Five milligrams of hydrocortisone acetate in 0.2 millilitre of the suspension were injected percutaneously with a 25-gauge needle into the tendo calcaneus on the right side, one centimetre above its insertion. 0.2 millilitre of 0.9 per cent sterile saline solution was injected with a separate needle into an identical site on the left side. The rabbits were fed with laboratory purina rabbit chow and observed daily for evidence of infection at the site of injection and for obvious rupture of the calcaneal tendon.

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<th>Time after injection of hydrocortisone</th>
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Forty-five minutes after injection of hydrocortisone into tendon. Normal collagen bundle continuous with disorganised collagen. (Haematoxylin and eosin, ×240.)

Forty-eight hours after injection of hydrocortisone into tendon. Necrosis of collagen with acute inflammatory response in a section close to the paratenon. (Haematoxylin and eosin, ×240.)
The rabbits were killed at varying intervals with intravenous injections of sodium phenobarbitone (Table 1). In each instance the tendo calcaneus with its paratenon was carefully dissected and the entire tendon from the musculo-tendinous junction to its insertion at the calcaneus was excised and fixed in 10 per cent formol saline. The fixed tendon was bisected longitudinally and embedded in paraffin. Sections were cut at 5 microns and stained with haematoxylin and eosin, elastic van Gieson, Masson's trichrome and Alcian blue. In selected cases, von Kossa's stain was used as well.

RESULTS

Immediate change (forty-five minutes after injection)—Sections from both hydrocortisone-injected and control tendons showed separation of collagen bundles. A few red blood cells were present in this space. Adjoining blood vessels were engorged with blood and a few polymorphs had emigrated into the tissue. At the site of hydrocortisone injection, a definite change in the appearance of the collagen bundles was seen. The normal parallel arrangement of the collagen fibres was lost and was replaced by a disorganised area of pale staining collagen in which nuclei of fibrocytes showed fragmentation and dissolution. The collagen bundles which had undergone this change showed a woolly, eosinophilic appearance (Fig. 1).

Acute inflammatory phase (twenty-four to seventy-two hours)—Control tendons showed no change in the appearance of the collagen bundles or damage to the fibroblasts. There was no increase in the number of polymorphs at the site of injection. Tendons injected with hydrocortisone showed areas of necrosis of collagen. These consisted of loose, structureless eosinophilic material interspersed in some areas with basophilic material. In longitudinal sections the necrotic collagen was continuous with normal collagen fibres. Nuclei of fibroblasts were not identified in the necrotic areas. The cellular response was varied. Lesions closer to the paratenon showed vasodilation and an acute polymorphonuclear cell response (Fig. 2). Lesions centrally placed in the tendon showed very little or no cellular response (Fig. 3).

**Fig. 3**
Centrally placed lesion forty-eight hours after hydrocortisone injection. Necrosis of collagen without significant inflammatory reaction. (Haematoxylin and eosin, x 240).
Stage of demolition (seventy-two hours to one week)—Necrotic areas in the experimental tendons showed an increase in basophilic staining. The majority of the polymorphonuclear cells in the exudate were necrotic and the cellular infiltrate was predominantly mononuclear in type (Fig. 4). Many foamy macrophages were present by seventy-two hours. In sections from two tendons there were microscopic foci of recent collagenous necrosis continuous with older basophilic necrotic areas. Nuclei of fibrocytes at the junction between necrotic and normal collagen showed karyorrhexis and pyknosis. Sections from control tendons did not show any abnormality.

Stage of repair—By four weeks, fibroblastic proliferation was prominent at the periphery of some lesions in the hydrocortisone-injected tendons. Control tendons did not show any abnormality. Repair of the necrotic lesion was more evident by six to eight weeks. The spindle-shaped outline of the lesion could be made out, although it had contracted in size. Proliferation of fibroblasts was usually present at the periphery of the lesion and this gradually extended for a variable distance towards its centre (Fig. 5). There were some lesions which did not show any recognisable attempt at repair, the spindle-shaped areas of necrosis being filled by an acellular, amorphous eosinophilic material. Calcification of necrotic areas of collagen, confirmed with the von Kossa's stain, was seen at the end of eight weeks in certain experimental tendons (Fig. 6).

DISCUSSION

The mechanism of tendon rupture after local infiltration of steroid is not clear. It has been ascribed to an inherent defect in the tendon (Cowan and Alexander 1961) or to minute tears in degenerating tendons where normal healing was inhibited by steroid therapy (Smaill 1961). Bedi and Ellis (1970) suggested that because of the avascular nature of the tendon, the steroid probably remained in it for a long time. This resulted not only in delayed maturation of fibrous tissue but also probably reduced the tensile strength of the tendon causing it to rupture with minimal effort. Whereas some of these explanations have theoretical merit, there is no objective evidence to support them.
FIG. 5
Six-week-old lesion, showing proliferation of fibroblasts at the periphery. Necrosed collagen is seen towards the centre. (Haematoxylin and eosin, ×240.)

FIG. 6
Calcification in an eight-week-old lesion in the tendon. (Von Kossa's stain, ×240.)
The present study demonstrates that infiltration of hydrocortisone into rabbit calcaneal tendons causes necrosis of collagen at the site of infiltration. An effect on the tendon was seen as early as forty-five minutes after the injection of hydrocortisone, when the collagen showed a woolly eosinophilic appearance after losing its parallel arrangement. Changes were also seen in the fibroblasts of the collagen which showed nuclear destruction and death of the cell. The necrosed collagen was seen to be continuous with normal collagen fibres at the periphery of the lesion. No necrosis of collagen was seen in any of the control tendons injected with saline solution.

The mechanism of the necrosis of collagen is not known. It may be due to a direct or an enzyme-mediated action by the hydrocortisone. In the skin it has been found that cortisol releases a protease, active at pH 7. This enzyme is believed to activate the skin collagenase and trigger the process of collagen breakdown (Woessner 1968). Although a similar mechanism may account for the breakdown of collagen in the present study, this is unlikely because the effect was seen as early as thirty to forty-five minutes after the injection of hydrocortisone. It is possible that the necrosis of collagen may be due to a direct action by the hydrocortisone.

The inflammatory response following the necrosis of collagen was varied. Lesions close to the paratenon showed an acute inflammatory response, whereas those centrally placed in the tendon showed little or no response. The process of repair also closely followed a similar pattern. In centrally placed lesions there was no repair of the lesion even after eight weeks. Peripheral lesions showed repair by proliferation of fibroblasts. This difference in inflammatory response and repair seems to be related to the proximity of the necrotic area to the vascular paratenon. It is also of interest that repair was often associated with dystrophic calcification.

CONCLUSIONS

This experiment demonstrates that infiltration of hydrocortisone into rabbit calcaneal tendons has a direct effect on the tendon, producing necrosis of collagen at the site of injection. The repair of the lesion so produced is incomplete even after eight weeks, and is often complicated by dystrophic calcification. Similar morphological changes may account for spontaneous rupture of tendons in patients receiving steroid infiltration.

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REFERENCES


