PREVENTION OF PERITENDINOUS ADHESIONS AFTER TENOLYSIS BY MEANS OF A CARBOXY-METHYLCELLULOSE (CMC), POLY-ETHYLENE OXIDE (PEO) BASED GEL: A LIGHT AND ELECTRON MICROSCOPE STUDY IN THE RABBIT

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SUMMARY

The prevention of peritendinous adhesions occurring after tenolysis is a major clinical issue. In the present study, the effectiveness of Dynavisc®, a new Carboxy-methylcellulose (CMC), Poly-Ethylene Oxide (PEO), NaCl and CaCl based gel, was tested in a rabbit model of tenolysis. In 20 male rabbits, the tendon of flexor digitorum communis muscle of the hindlimb was surgically damaged all around its circumference for a length of 3 cm. In 10 animals, Dynavisc® was applied around the injured tendon segment before suturing the skin. Rabbits were sacrificed 45 days after surgery. Formation of peritendinous adhesions and regeneration of the tendon sheaths was quantitatively assessed by macroscopic, microscopic and ultrastructural analysis.

In Dynavisc®-treated tendons, peritendinous adhesions were limited and the presence of a well regenerated tendon sheath was clearly detectable while in un-treated tendons large adhesions sites all around the tendon surface were detectable and cleavage planes were much less represented. The typical stratification of the peritendinous sheaths was almost absent in the latter group. Quantitative assessment showed that Dynavisc®-treated tendons scored significantly better regarding both peritendinous adhesions and tendon sheath regeneration.

This study demonstrates that local Dynavisc® application not only prevents adhesion formation after tenolysis, but also promotes normal healing of the peritendinous structures resulting in a well regenerated synovial sheath.

These data together provide more evidence on the clinical applications of the product in tendon surgery, especially when an extended damage on tendon sheath is present.

INTRODUCTION

Tendons are anatomic connective structures, interposed between muscles and bones, that transmit the force created in the muscle to bone, and, in this way, make joint movement possible (Kannus, 2000). Because of their moving under tension near various other tissues and organs, they are subjected to friction and thus they are surrounded by enveloping structures which protect them and facilitate their movements. These surrounding structures are called peritendinous synovial sheaths (Strocchi et al., 1985) and form access tunnels for tendons at bone surfaces or other anatomic structures that might cause friction (usually around the tendons of the hand and feet). Under a fibrous layer, there are two serous sheets (parietal and visceral) which form a closed duct including peritendinous fluid for lubrication. In some tendons, there can be a peritendinous fibrillar sheath, composed of a loose fibrillar tissue, which functions as an elastic sleeve allowing free movement of the tendon against surrounding tissues.

From a clinical point of view, the main concern of the surgeon is the development of adhesions between tendon and the surrounding tissue after tendon repair and/or tenolysis (Kakar et al., 1998). Tendon injury firstly results in onset of an inflammatory response whereas formation of adhesions and scar tissue, which eventually prevent tendon gliding, occur later.

Various methods have been proposed to prevent peritendinous adhesions after tenolysis. The main goal of all the strategies employed so far has been to create a potential barrier between the healing tendon and the surrounding wound in order to reduce the inflammatory response around the tendon surface and also to limit the subsequent formation of scar tissue which eventually leads to the formation of peritendinous adhesions. The ideal material for accomplishing this goal should also have the property of not interfering with the re-formation of the normal tendon synovial sheath, or even facilitate this repair process.

Multiple different strategies have been experienced so far.

Some authors have tried to use biological membranes derived from other tissues (tissue engineering) wrapping them around the lesion site in order to create a peritendinous barrier.

Strauch and co-workers (1985) have successfully employed autogenous vein grafts during primary tendon repair with significant greater functional return in comparison to control patients. Other attempts with biological membranes include peritoneum (Oei et al. 1996), pericardium (Sungur et al., 2006), fascial grafts (Peterson et al., 1990), buried adipofascial flaps (Parodi, 2006) and island fascial flaps (Tham, Riccio et al 1996; Riccio et al. 2007).

The last autogenous graft employed to prevent scar adhesions after tenolysis and neurolysis is the fat grafting technique (Damgaard, 2010; Vaienti, 2010, Vaienti 2012).

In chickens, also amniotic membrane wrapping proved to be effective in the prevention of peritendinous adhesions after tendon repair (Demirkan et al., 2002).
Coating the injury site with fibrin sealant has also been shown to exert beneficial effects in reducing post-surgical tendon adhesion formation (Frykman et al., 1993; Jones et al., 2002).

Whereas autogenous transplantation of biological tissues with a different origin has advantages, in particular related to availability at low cost, with the aim of achieving a barrier which mimics more closely normal tendon sheaths, various synthetic materials have also been investigated. Polytetrafluoroethylene, millipore cellulose tubes, and silastic membranes (Peterson et al., 1990), hydroxyapatite or alumina (Siddiqi et al., 1995) and polyethylene membranes (Hanff et al., 1998) were various types of mechanical barriers that has been successfully used to prevent the post-surgical adhesions of tendons.

A further approach that has gained particular attention during the last decades is the employment of hyaluronic acid or its derivatives. As regards peritendinous adhesions after tendon injury, it has been shown that hyaluronic acid application around a repaired tendon reduces post surgical adhesion formation (Thomas et al., 1986; Hagberg and Gerdin, 1992; Isik et al., 1999; Moro-oka et al., 2000; Nishida et al., 2004; Akasaka et al., 2005, 2006). Interestingly, application after tendon surgery of Human Amniotic Fluid (HAF), which contains high molecular weight hyaluronic acid in high concentrations and hyaluronic acid-stimulating activator (Dahl et al., 1983, 1986), alone (Ozgenel et al., 2001) or in combination with hyaluronic acid (Ozgenel, 2004), is also effective in preventing peritendinous adhesions.

Recently, it has been shown that local application of a hyaluronic acid autocross-linked derivative with high safety and biocompatibility profiles, namely ACP, significantly reduces post surgical adhesions in various sites. For instance, De Iaco et al. (1998) and Belluco et al. (2001) have shown that ACP is effective in preventing adhesions in clinics after abdominal surgery, while other authors have demonstrated its efficacy after knee surgery in a preclinical model (Brunelli et al., 2005) and nerve reconstruction both in preclinical and clinical setting (Smit et al., 2004; Dam-Hieu et al., 2005; Atzei et al., 2007).

Moreover, a multicentre clinical trial has shown the efficiency of a autocross-linked hyaluronan based gel in the prevention of the recurrence of adhesions after tenolysis of flexor tendons in zone II of the hand (Riccio M, et al., 2010).

Yet, bioresorbable membranes made of Seprafilm (combination of sodium hyaluronate and carboxymethylcellulose) have also shown to be effective in preventing peritendinous adhesions in a rabbit model (Menders et al., 2004).

The present study was designed to assess the effectiveness of Dynavisc®, a resorbable gel-formulated adhesion-barrier (a carboxy-methylcellulose, poly-ethylene oxide based gel), in the prevention of peritendinous adhesions in an experimental model of tenolysis in the

rabbit, specifically focusing, for the first time, on result evaluation at histological and electron microscopy level.

Another aim of the study was to acquire more information on the biological role of Dynavisc® in the regeneration of the tendon synovial sheath, which plays a key role in the perspective of a good recovery of the tendon function.

METHODS

Twenty-five adult male New Zealand rabbits weighting 2kg to 3kg were used in this study. The rabbit tendon experimental model was selected because rabbit tendons, in comparison to rat tendons, are larger and thus more similar to human tendons. Yet, the tendon of flexor digitorum communis muscle of the hind limb was selected since it is a long tendon, easily accessible surgically and with well defined peritendinous sheath. Finally, we selected a type of lesion which mimics a typical tenolysis in clinical conditions, i.e. a 1.5 cm-long scrubbing of the tendon surface, proximal and distal to an incision corresponding to about 40% of the tendon diameter.

In this experimental model, we tested the hypothesis that application of Dynavisc® immediately after lesion could have a protective effect on peritendinous post-operative adhesion formation as well as a facilitating effect on the regeneration of the tendon sheaths by reducing peritendinous friction during movements. The hypothesis was tested with a 3-level battery of evaluation systems. First, macroscopic examination at the time of tendon withdrawal to assess the gliding function of the tendon. Second, assessment of adhesions and peritendinous tendon sheaths regeneration by both light and electron microscopy examination. Based on macroscopic, microscopic and ultra-structural examination a 4-point semi-quantitative grading system was adopted in order to determine, in each animal, the degree of adhesion formation and of synovial sheaths regeneration. The scoring of each sample was assigned by two independent observers and results were presented as the mean between the two scores assigned. Adhesion formation scoring was carried out as follows: 0-severe adhesions; 1-moderate adhesions; 2-few adhesions; 3-no adhesions. Synovial sheath regeneration scoring was carried out as follows: 0-very poor regeneration; 1-poor regeneration; 2-moderate regeneration; 3-good regeneration.

Adequate measures were taken to minimize pain and discomfort taking into account human endpoints for animal suffering and distress. All procedures were performed with the approval of the local Institution's Animal Care and Ethics Committee, and in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). Animals were housed in large cages in a temperature and humidity controlled room with 12-12 h light / dark cycles, and were allowed normal cage activities under standard laboratory conditions. The animals were fed with standard chow and water *ad libitum*.

Surgery was carried out with the animals placed prone under sterile conditions and the skin from the dorsal aspect of the left tight shaved and scrubbed in a routine fashion with

antiseptic solution. Under deep anaesthesia (Zoletil 100 01.ml, Rompum 0.5ml, saline solution 3.5ml, 30mg/1kg body weight, intravenous), the tendon of flexor digitorum communis was approached and exposed proximal to the ankle.

In twenty rabbits, a 3 cm-long segment of the tendon sheath was then damaged surgically all around its circumference mimicking the tenolysis condition occurring in patients (figure 1). In the midway of the injured tendon segment a surgical incision corresponding to 40% of the tendon diameter was done in order to allow the exact identification of the lesion site at time of withdrawal. The animals were then divided into two groups (n=10); in group 1, 1 ml of Dynavisc® was applied around the injured tendon segment; in group 2, 1 ml of saline solution was applied around the tendon in the same way as for group 1. The skin was then closed with 4/0 resorbable sutures. The remaining five rabbits were used as controls.

After surgery, animals were kept in single cages and given 300.000 units of penicillin intramuscular along the first three postoperative days to prevent infections. No hindlimb immobilization was adopted in order to allow tendon movements along the postoperative. After 45 days, animals were euthanized with a 300mg/kg pentobarbital overdose and injured tendons were approached and carefully exposed to permit macroscopic examination of gliding movements and peritendinous adhesions.

At time of withdrawal, after macroscopic scoring of adhesions, the tendons were withdrawn and immediately divided into two 1cm-long samples, one proximal and one distal to the tenotomy site, which were then processed for light and electron microscopy observation respectively.

For light microscopy, tendon samples were fixed in 10 % formalin for 12h and then washed in phosphate buffer saline (PBS) until embedding. The specimens were dehydrated and embedded in paraffin and cut at 6-8 µm perpendicular to the tendon axis. Sections were stained with hematoxylin and eosin and Masson trichrome staining and observed in a DM400 microscope equipped with DFC320 digital camera and IM1000 image manager system (Leica Microsystems, Wetzlar, Germany),

For electron microscopy, tendon samples were fixed in 2.5% gluteraldehyde (Fluka, St. Louis, MO, USA) and 0.5% saccharose in 0.1 M Sörensen phosphate buffer for 6-8 h (Raimondo et al., 2006). The specimens were then washed in 1.5% saccharose in 0.1 M Sörensen phosphate buffer for 6–12 h, post-fixed in 2% osmium tetroxide, dehydrated and embedded in Glauert's embedding mixture (Di Scipio et al., 2008), which consists of equal parts of Araldite M and Araldite Härter, HY 964 (Merck, Darmstadt, Germany), supplemented with 2% of the accelerator DY 064 (Merck, Darmstadt, Germany). The plasticizer dibutyl phthalate was added at 0.5%.

Semi-thin sections (1 um) were then cut before cutting ultrathin sections (70-100 nm) using a Leica Ultracut UCT. Semi-thin section were stained with toluidine blue for 2-3 minutes and observed in a DM400 microscope equipped with a DFC320 digital camera and a IM1000 image manager system (Leica Microsystems, Wetzlar, Germany), while ultrathin

sections were stained with uranyl acetate and lead citrate and examined in a JEM-1010 transmission electron microscope (JEOL, Tokyo, Japan).

Statistical analysis of quantitative assessment of adhesion formation and synovial sheath regeneration scorings were performed using one-way analysis of variance (ANOVA) test. Statistical significance was established as $p < 0.05$.

RESULTS

Figure 2 shows the results of the macroscopic observation of injured tendons at time of withdrawal, which showed the presence of less peritendinous adhesions at the site of tenolysis in Dynavisc®-treated tendons (figure 2A) in comparison to un-treated controls (figure 2B).

Figure 3 shows the histological comparison between a normal tendon (fig. 3B-C) and injured tendons from the two experimental groups (fig. 3B-C). Peritendinous sheaths in Dynavisc®-treated tendons (fig. 3B) look similar to normal tendons (fig. 3A), while in un-treated tendons (fig. 3C) the surroundings were more dense, less organized and showed large adhesion sites. While in Dynavisc®-treated samples peritendinous adhesions were limited and the presence of a well regenerated synovial sheaths was clearly detectable (fig. 4A-E), un-treated tendons showed large adhesions sites all around the tendon surface (fig. 4F-H).

Electron microscope examination of the synovial sheaths (fig. 5) showed that in Dynavisc®-treated tendons the synovial sheaths were organized in stratified layers with large cleavage planes (fig. 5A) similar to those that are detectable in normal tendons sheaths (fig. 5B). Yet, while collagen fibers were more densely packed than in normal tendons, nonetheless they were organized in parallel fascicles (fig. 5C) and show the typical size differences between the inner visceral layer (fig. 5D) and the external fibrous layer (fig. 5E).

By contrast, in un-treated tendons cleavage planes were much less represented and the typical stratification of the peritendinous sheaths was less clear (fig. 5E,F). Yet, the presence of large bundles of variously sized collagen fibers densely packed and without any clear orientation can be detected (fig. 5G,H).

The differences observed at both macroscopic (assessment of the gliding function), microscopic and ultrastructural level were quantified by means of the grading system described in the material and methods, with respect to two parameters: 1) Presence of peritendinous adhesions; 2) Regeneration of a tendon sheath with respect to normal structure.

Results of the quantitative assessment of peritendinous adhesions at the site of tenolysis showed that Dynavisc®-treated tendons scored on average 1.7 ± 0.7 while un-treated tendons scored 1.1 ± 0.5. Statistical analysis by mean of ANOVA showed that this difference is significant ($p < 0.05$). Similarly, the results of the quantitative assessment of tendon sheath regeneration at the site of tenolysis showed that Dynavisc®-treated tendons

scored on average 1.6 ± 0.5 while un-treated tendons scored 1.1 ± 0.6. Statistical analysis by mean of ANOVA showed that this difference is significant ($p < 0.05$).

DISCUSSION

Tenolysis, and in general tendon surgery, is followed by an inflammatory response which leads to scar tissue formation, hinders regeneration of the synovial sheath and eventually results in interference with tendon gliding and limiting related movements, e.g. digital flexion (Kakar et al., 1998). Therefore, extensive efforts have been carried out over the last twenty-five years to find out effective ways to solve this clinical problem, i.e. to prevent peritendinous adhesions. In the search for effective therapeutic approaches to prevent post-injury tendon adhesions, several types of biological and synthetic materials have been designed and tested both experimentally and clinically. The different methods that have been proposed to prevent peritendinous adhesions so far have been based on the employment of synthetic non-resorbable barrier or biodegradable materials of natural origin.

Recently, a resorbable gel-formulated adhesion-barrier has been developed (Dynavisc®). Results of the present study showed that application of Dynavisc® after tenolysis in a rabbit model is effective in preventing post-surgical peritendinous adhesions. Data obtained in the present study add new information to the literature since we focused also on the healing of tendon surroundings (synovial tendon sheaths) showing that the prevention of adhesions is accompanied by a better synovial regeneration as shown by ultra-structural observation. It can thus be tentatively proposed that one of the mechanisms of action of Dynavisc® in the prevention of peritendinous adhesions, which is the ultimate goal after tenolysis, depends on its role in facilitating the reorganization of the tendon sheaths. This effect can be mediated by the fact that Dynavisc® compensates the loss of synovial fluid (Wiig et al., 1996) that occurs after tenolysis and is necessary for healing of peritendinous sheaths (Hagberg and Gerdin, 1998).

CONCLUSIONS

The results of the present study support the conclusion that local Dynavisc® application around the tendon is indicated for the prevention of adhesions after tendon surgery. Employment of this product can be indicated especially when an extended damage on tendon sheath is present (i.e. tenolysis) and thus the positive effects of this resorbable anti-

adhesion gel on the regeneration of the peritendinous synovial sheaths are particularly needed.

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FIGURE LEGENDS

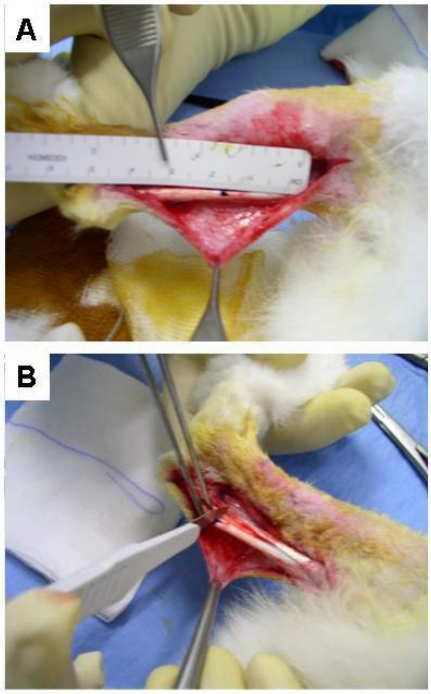
Fig 1. Surgical steps. A. Approach to the tendon. B. Tendon damage is performed. C. Dynavisc® application to tendon injury site.

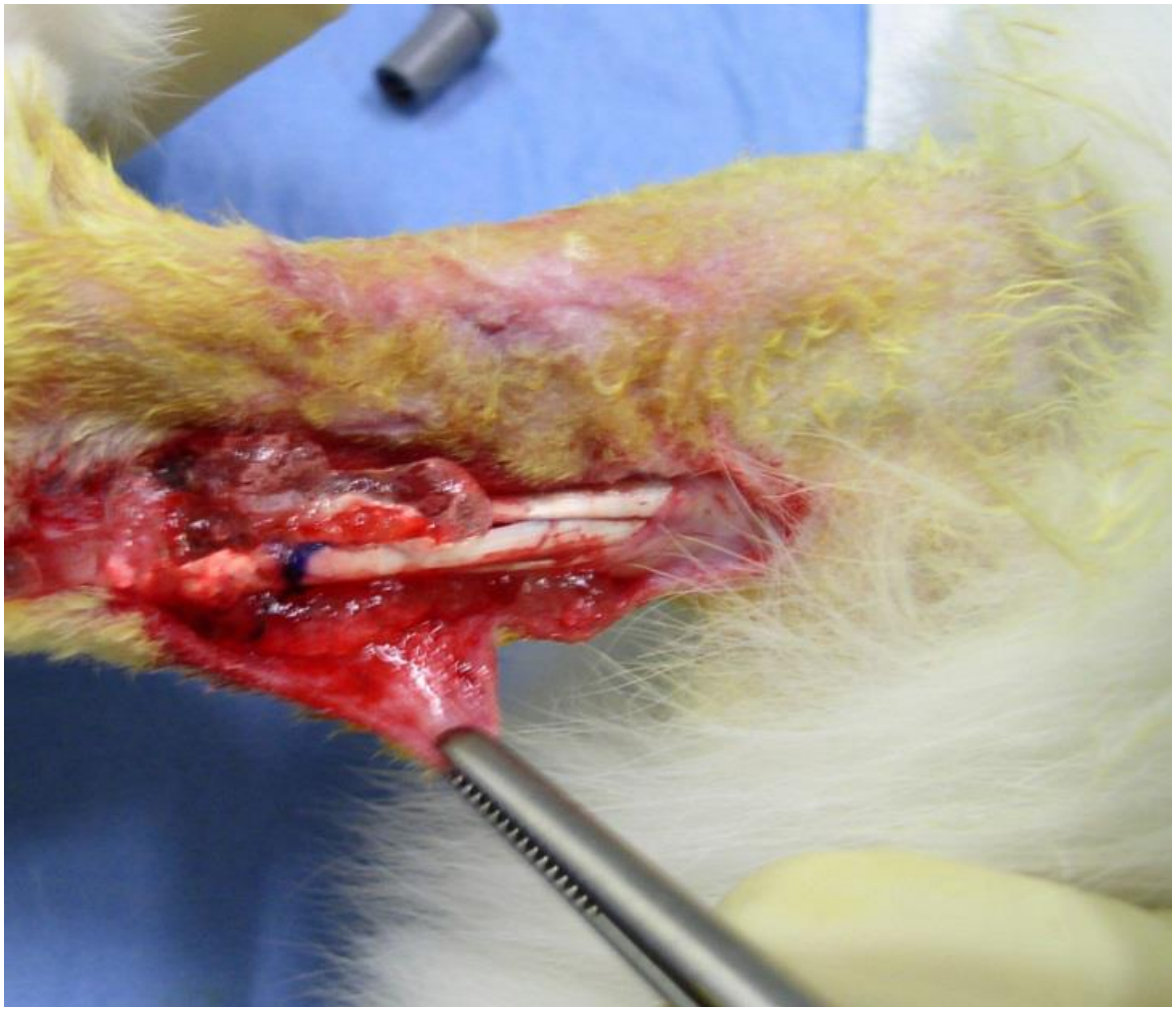
Fig 2. Macroscopic analysis of tendon adhesions at time of withdrawal. A-B. Dynavisc® group. C-D. Control un-protected group.

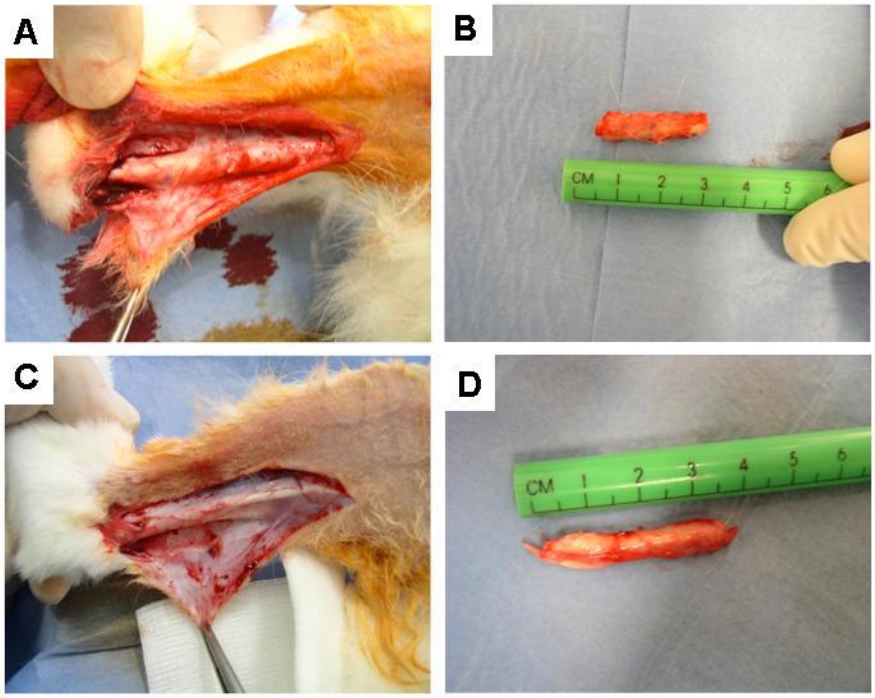
Fig 3. Low magnification light microscopy analysis after toluidine blue staining. A. Normal undamaged tendon. B. Dynavisc® group. C. Control un-treated group. Magnification = 100x.

Fig 4. High magnification light microscopy analysis after toluidine blue (A,B,E,F) and ematoxylin and eosin (C,D,G,H) staining. A-D. Dynavisc® group. E-F. Control un-treated group. Magnification: A,C,E,G = 400x; B,D,F,H = 900x.

Fig 5. Electron microscopy analysis. A. Normal undamaged tendon. B-E. Dynavisc® group. F-H. Control un-treated group. Magnification: A-B = 50,000x; C-E = 60,000x; F = 10,000x; G = 30,000x; H = 15,000x; I = 25,000x.







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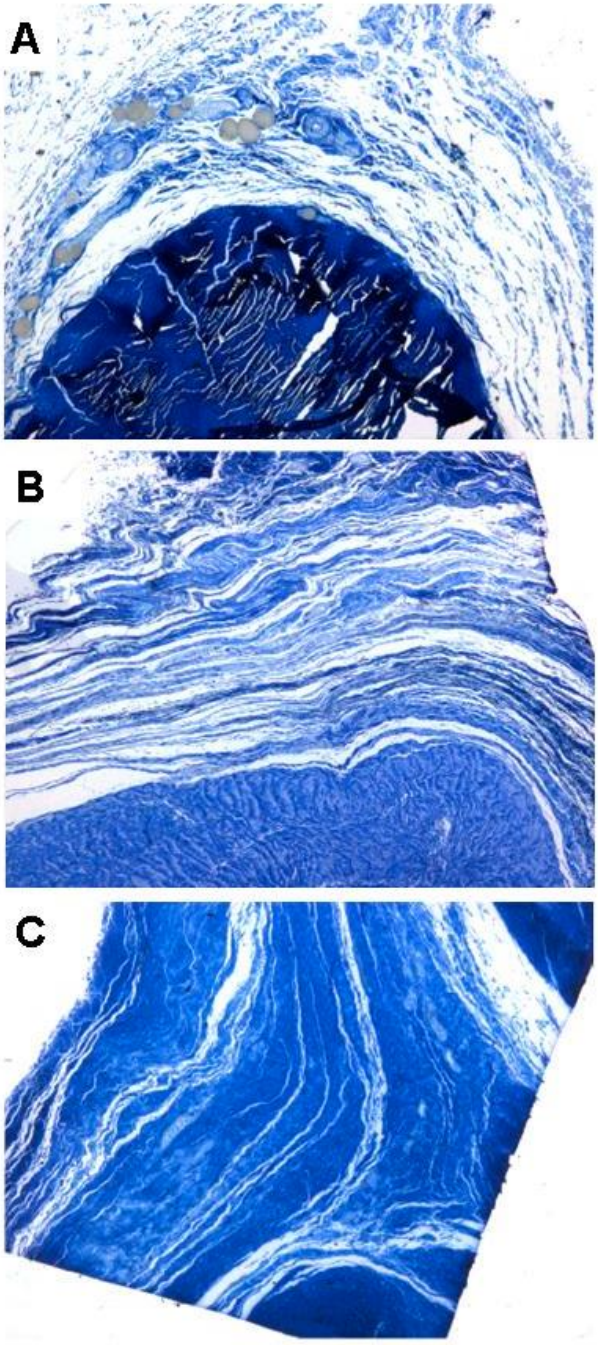
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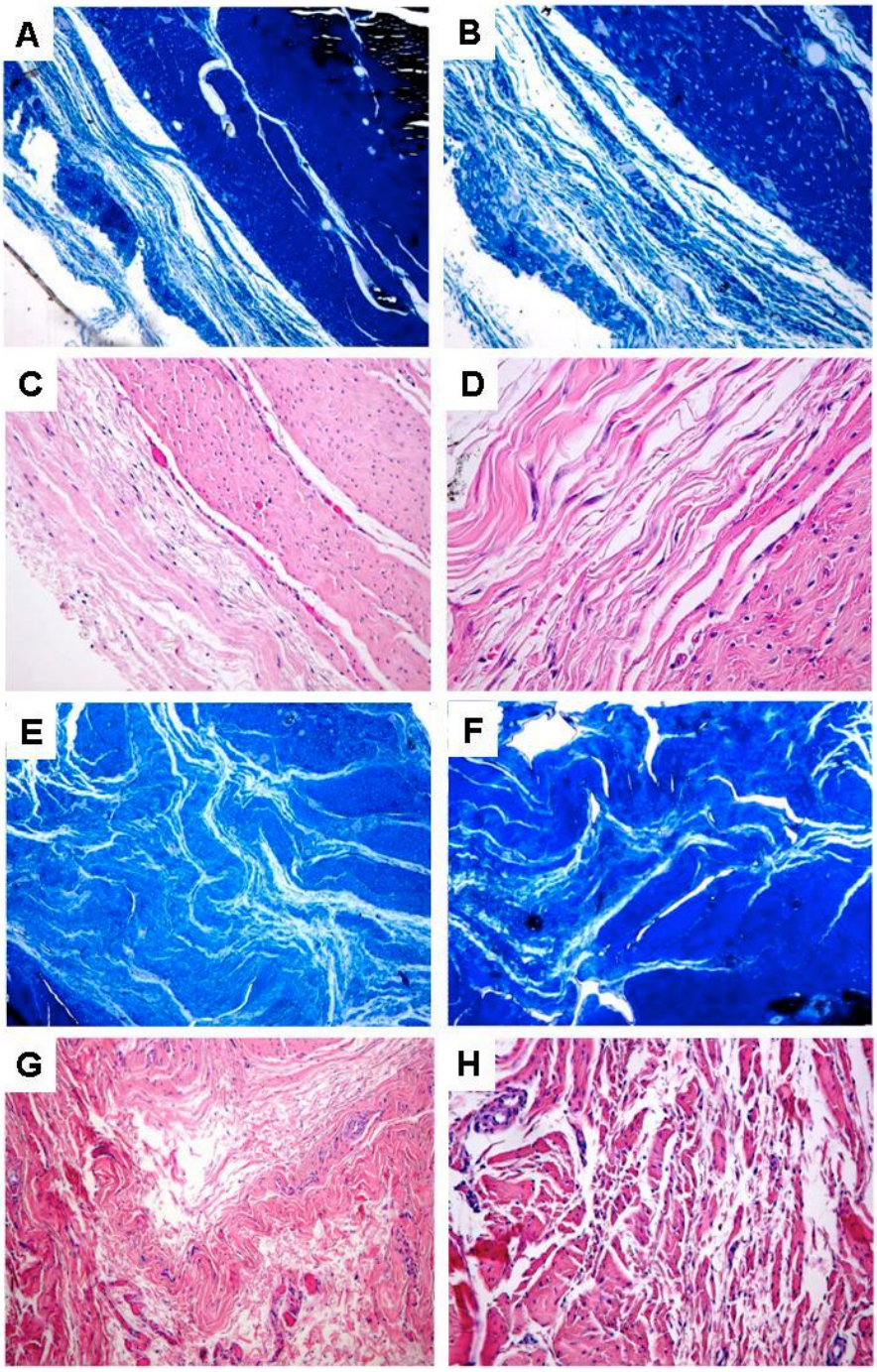
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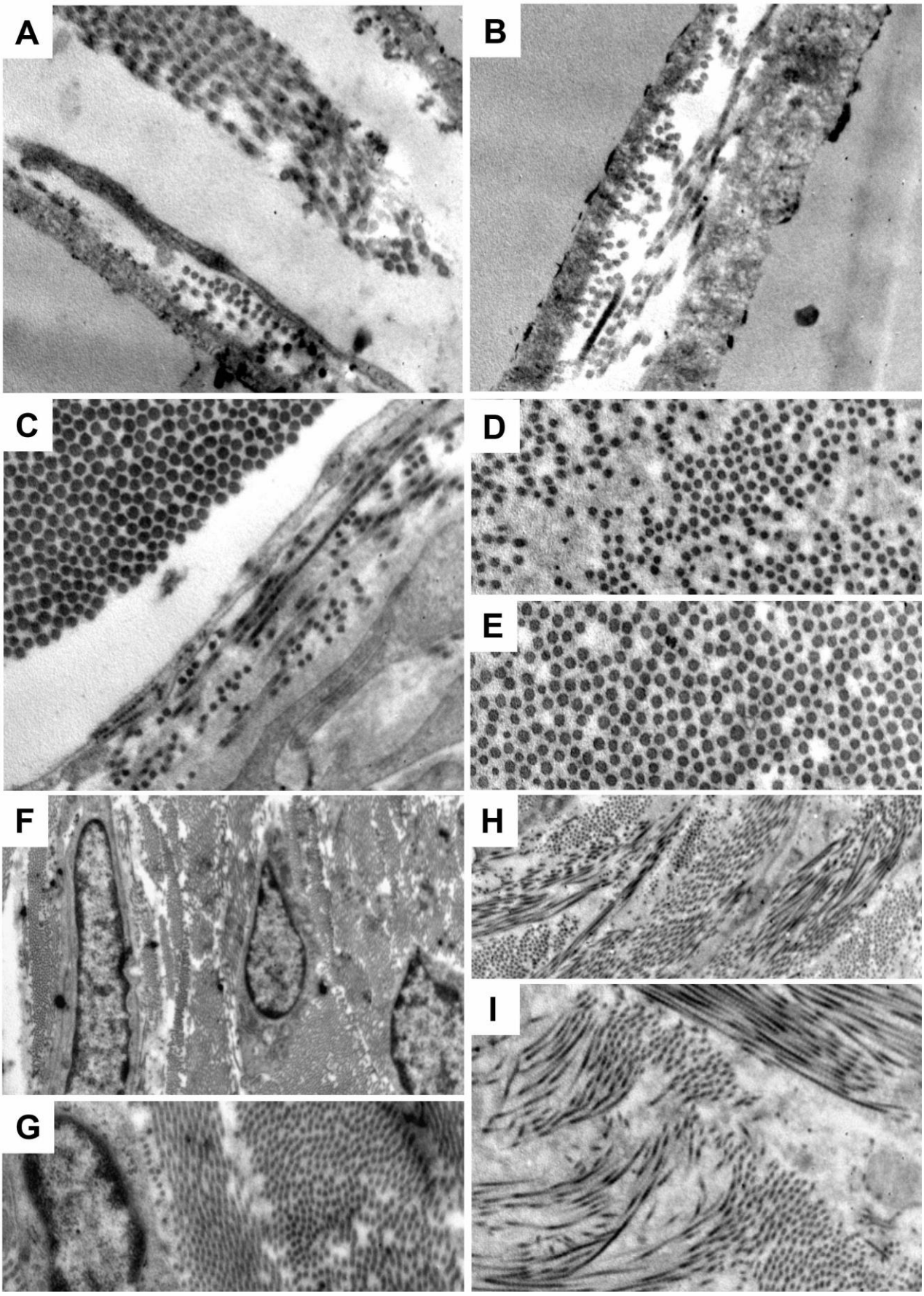
A
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