Animal models of tendinopathy

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Abstract

Purpose. The term tendinopathy describes non-ruptured tendon injuries. While several important studies have evaluated the aetiology, pathogenesis, and treatment of this common condition, further study is needed. Several animal models, which allow for full tissue evaluation on different organizational levels and stages of disease, have been used to investigate tendinopathy.

Method. A literature review was conducted to identify and evaluate animal models that have been developed and used to study the aetiology and pathology of tendinopathy.

Results. Animal models of tendinopathy fit into two general categories based on the mode of injury application: (i) models that induce tendinopathy through a change in the mechanical environment, and (ii) models that induce tendinopathy through a chemical agent. The cost, difficulty, invasiveness, reproducibility and time required to induce injury in these models varies. Mechanically-induced models are beneficial since they induce injury through repetitive mechanical loading, similar to how tendinopathy is believed to develop in the human condition. Chemically-induced models are beneficial by allowing for the study of the interplay among inflammatory cells, mechanical loading and tissue healing.

Conclusion. Further work is needed to fully characterize and understand tendinopathy. Appropriate animal models provide a greater understanding of human tendinopathy, leading to better prevention and treatment.

Keywords: Tendon, animal model, tendinopathy, overuse, collagenase

Introduction

Tendon injuries are a common problem, resulting in over two million doctor office visits in the USA alone in 2001 [1]. It has been estimated that overuse-type injuries account for 30–50% of all sports-related injuries and nearly half of all job-related illness in the USA [2–4]. Historically, the term tendinitis (or tendonitis) has been used to describe non-ruptured tendon injuries with associated inflammation [5–8]. More recently, the term tendinosis has been used to describe a degenerative, rather than inflammatory, process since several studies observed a lack of inflammation with this type of injury [9–20]. It has also been suggested that inflammation may occur early in the injury, but then is quickly superseded by a degenerative response [13]. Since the pathology remains unclear, the term tendinopathy is frequently used as a generic term to describe non-ruptured tendon injuries. Signs of tendinopathy include disorganization, thinning and microtearing of collagen fibres [10–13,17,21–23], extensive neovascularization and vascular ingrowth [9,10,12,13,17,22–24] increased interfibrillar glycosaminoglycan [10,12,13,17,21–23,25], regulation of matrix metalloproteinases and their inhibitors [18,26–30], and increased glutamate production [14–16]. In addition, regions of both hyper- and hypo-cellularity have been described and fibroblasts have been observed to lose their spindle shape and become more round and chondrocyte-like [11,13,17,21–23]. Finally, tendinopathy leads to altered mechanical properties [31], and studies that evaluated ruptured tendons observed degenerative changes in nearly every specimen, indicating that tendinopathy may precede, and perhaps cause, tissue failure [32,33].

While the studies described above provide characteristics of tendinopathy, the aetiology of tendon
Degeneration and injury remains unclear. One reason is that human tissue can normally only be examined during the end-stage chronic pathology. It is difficult, if not impossible, to obtain early stage pathologic tendon tissue because these injuries are often initially asymptomatic or treated non-invasively. By providing tissue during all stages of tendinopathy, animal models provide an excellent approach to investigating tendinopathy. An animal model allows a reproducible and consistent injury to be induced and the result of that injury can be monitored, evaluated and treated over time in a controlled and quantifiable manner. In addition, animal models allow for invasive evaluation at the organ, tissue, cellular and molecular levels [19,34]. This manuscript will review and evaluate animal models that have been developed in order to better understand the aetiology and pathology of tendinopathy. Two general categories of animal models will be discussed based on the mode of injury application: (i) models that induce tendinopathy through a change in the mechanical environment, and (ii) models that induce tendinopathy through a chemical agent.

Mechanically-induced

Active participation models

The method most frequently used to induce tendinopathy through a mechanical stimulus is repetitive treadmill running. In particular, this method has been used to evaluate injury to the supraspinatus tendon of the rotator cuff [35]. Rats were subjected to a repetitive exercise protocol that consists of treadmill running at 17 m/min on a 10° decline for 1 hour/day, 5 days/week. After several weeks of treadmill running, the supraspinatus tendons in exercised animals demonstrated significant and dramatic changes compared to controls [36]. The tendons had larger than normal cross-sectional areas and inferior mechanical properties, including decreased maximum stress and decreased modulus at all time points (Figure 1). The decrease in material properties occurred early and remained consistently below control throughout the duration of the experiment.

In addition to changes in material properties, histological results also demonstrated a response to overuse in all parameters measured. Compared to control, the experimental tendons exhibited increased cellularity, vascularity, glycosaminoglycan content, and collagen fibre disorganization (Figure 2B–2D) [37]. Tissue deterioration was greater at longer time points, indicating increased damage with continued exposure to the treadmill protocol (Figure 2A) [36,37]. In addition, cell shape was altered and round chondrocyte-like cells were observed proximally and superficially at later time points, suggesting the possibility of fibrocartilaginous metaplasia in the tendon as a result of overuse (Figure 2C). This concept is supported by the up-regulation of cartilage-specific genes, such as aggregan and type II collagen (Figure 3), and down-regulation of tendon-specific genes as a result of the same treadmill running protocol [38]. The presence of chondrocytic cells and the over expression of cartilage genes suggests that the tendon is converting toward a fibrocartilage phenotype. These changes due to repetitive loading are potentially exacerbated by repeated compression of the tendon against the acromial arch as it passes through this structure, similar to what is believed to occur in the human condition.

Other groups of genes, including glutamate signalling and stress response genes, were also observed to be significantly regulated with this treadmill running [39]. Several receptor genes involved in the glutamate signalling pathway (mGluR5, mGluR6 and NMDAR1) were measured to be up-regulated compared to controls. This pathway has been shown to be up-regulated in bone in response to mechanical loading and may play a similar role in tendon as repetitive loading directly results in tendinopathy [40]. In addition, several stress response genes related to excitotoxicity and

![Figure 1](https://example.com/figure1.png)
apoptosis (HSP27, HST70, and FLIP) were shown to be highly up-regulated with overuse. The up-regulation of these anti-apoptotic stress genes suggests that they may play an important role in minimizing the development of tendinopathy. In support of this view, significantly increased amounts and activity of insulin-like growth factor 1 (IGF-1) after long periods of running have been demonstrated [37]. IGF-1 exerts a proliferative and prosurvival effect on tenocytes and may also be involved in stimulating collagen synthesis and regulating chondrogenesis. In addition to the presence of this anti-apoptotic growth factor, no regions of cell death were observed throughout the time course of this study.

Evidence of inflammation, angiogenesis and degradation in this rat model of rotator cuff tendinopathy has also been examined. The pro-inflammatory genes five-lipoxygenase activating protein (FLAP) and cyclooxygenase-2 (COX-2) demonstrated increased expression at early and moderate time points, with a return towards normal values at later time points [41]. In addition, several inflammatory genes were up-regulated while others were down-regulated after moderate repetitions of treadmill running, most of which were genes corresponding to immunoglobins and inflammatory cell receptors [39]. However, other studies have described a general lack of inflammation [37,38].

Regarding angiogenesis, one study demonstrated up-regulated expression of the angiogenic factors vascular endothelial growth factor (VEGF) and von...
Willebrand factor (VWF) [41]; however other studies have observed a general lack of neovascularization [37,38]. One additional molecule that has been evaluated in the treadmill running rat model is nitric oxide (NO), a highly reactive free radical that is produced by enzymes called nitric oxide synthases (NOS). Expression levels for all three isoforms of NOS were increased with overuse treadmill activity [42]. Since high levels of NO have been associated with degradative processes but also have been shown to promote wound healing responses, it is unclear what role NO plays in tendinopathy. NO may play a dual role, where local concentration determines the degenerative or reparative role of NO [42]. However, further studies are needed to clarify the role of NO in tendinopathy. Despite the large number of studies using this rat treadmill running overuse model, in general, the biological response to the overuse stimulus requires further analysis in order to completely understand the aetiology and pathogenesis of the overuse condition.

In addition to treadmill running, another model was developed to mechanically induce degenerative changes including tendinopathy through repetitive reaching and grasping [43]. In this model, animals were unable to maintain the baseline reach rate, and motor behaviour and control deteriorated over time. A general inflammatory response was evidenced by increased infiltrating macrophages (ED1-IR) in connective tissue (including tendon) from all limbs and a local inflammatory response was seen by increased resident macrophages (ED2-IR) in the forelimb tendons of the reaching limb only. In addition, collagen fibre disruption was observed after several weeks of performing the reaching task. Therefore, this model of repetitive motion overuse caused both functional changes and inflammatory responses after several weeks of activity.

Passive participation models

Different from active behaviours such as running and reaching, several models have induced tendinopathy mechanically through passive participation of the animal. One such model used a kicking machine to apply passive flexion and extension to the ankle joint of rabbits under anaesthesia, while simultaneously inducing active muscle contraction using electrical stimulation [44]. After being subjected to this protocol, the Achilles tendon of the exercised legs showed evidence of degeneration including fibrillation and altered cell nuclei. The paratenon exhibited increased numbers of fibroblasts and capillaries, as well as edema and infiltration of inflammatory cells. Thus, simultaneous muscle stimulation and passive motion were able to incite histopathological changes in tendon and paratenon after several weeks of application.

Results were quite different in a study which utilized a slightly modified technique, where a kicking machine was used but muscle stimulation was delivered via implanted nerve cuff electrodes on the tibial nerve [45]. Different from the previous study, this study utilized a more physiologically-relevant frequency of loading, skeletally-mature rabbits, and measured load levels during testing. Results after 11 weeks indicated no gross or microscopic changes in the loaded Achilles tendons, where the matrix organization, cellularity, vascularity, water content and DNA concentration were not different from control tendons. In addition, very few of the evaluated genes showed significant changes as a result of loading. The experimental limb had small increases in the gene expression of collagen I and III and the pro-inflammatory cytokines IL-1β and TNF-α. The only consistently down-regulated gene was IGF-II. In contrast to the prior study, no histological signs of inflammation or degeneration were observed in the loaded Achilles tendons. Subsequently, this lack of degeneration and damage was confirmed in a study that used a kicking machine with muscle stimulation in rats [34]. Macroscopically, there were no differences between control and experimental tissues after 7–11 weeks of the exercise protocol. Functional, histological, and immunohistochemical analyses demonstrated discrete alterations in a few of the exercised tendons; however these changes were not widespread and were proliferative and reparative rather than degenerative in nature. Therefore, up to 11 weeks, this protocol did not result in consistent changes corresponding to tendinopathy.

Recent work has used muscle stimulation alone to evaluate microstructural and molecular changes in the rabbit flexor digitorum profundus (FDP) tendon at the medial epicondyle as a result of cyclic loading [2,46]. Under anaesthesia, the FDP muscle was stimulated for 80 total hours of loading. The tendons were examined for microtears (3–300 μm² area) and evaluated for the amount and location of several growth factors. The stimulated FDP tendons demonstrated greater tear size, density and total tear area compared to contralateral, unloaded tendons, with the outer regions demonstrating greater damage than inner regions. The density of cells staining for VEGF, VEGFR-1 (a receptor for VEGF), and CTGF was also increased in the loaded tendons, with the highest densities in all three occurring at the outer region of the insertion site. VEGF and VEGFR-1 are angiogenic factors, while CTGF may stimulate angiogenesis and matrix production. These results are consistent with the treadmill running model described earlier, where the expression of VEGF was also up-regulated as a result of overuse [41]. In this muscle stimulation model, it remains unclear whether microtears initiate the expression of
growth factors, or whether the presence of growth factors alters tendon structure leading to microtear damage, thus requiring further study.

Distinct from previous work, two models have been developed that use a single, rather than repeated, application of an injury to induce tendinopathy. In one study, an injury was created by dropping a weight on the exposed Achilles tendon of rats under anaesthesia [47]. Results describe the progression of the healing response from 2 hours to 4 weeks post-injury. The immediate response included hypercellularity including many inflammatory cells, which led to sub-acute inflammation in the tendon and paratenon. By 1 week post-injury, acute inflammation had subsided and granulation tissue was observed along with mild inflammation. At the end of 4 weeks, the tendon demonstrated a normal appearance and no inflammation, although collagen alignment was not yet entirely normal.

A novel technique was recently developed where rat patellar tendons were fatigue loaded in vivo [48,49]. Under anaesthesia, small incisions were made at the knee and custom clamps were secured to the tibia and patella allowing a load to be applied to the patellar tendon. The protocol consisted of a single application of cyclic loading and animals were sacrificed one to two weeks post-loading. Histology results at one week were variable, with decreased cellularity and matrix disorganization in some regions and increased cellularity and repair in others. At two weeks, the cross-sectional area was increased and the ultimate stress and modulus were decreased in the loaded tendons compared to controls. MMP-3 (a matrix degrading enzyme) and CITED2 (a transcriptional regulator) were expressed in patellar tendons loaded to low and moderate fatigue levels [50]. A low level of fatigue increased MMP-3 expression slightly, while a moderate level of fatigue greatly increased expression. CITED2 demonstrated an inverse expression pattern and was shown to directly regulate MMP-3 expression. Since the histological and mechanical results and the MMP regulation observed in the loaded tendons are similar to conditions in human tendinopathy, this model may be useful for future evaluation.

Extrinsic alteration models

It has been proposed that tendinopathy and degeneration in the rotator cuff may be due to, or exacerbated by, extrinsic causes, specifically through compression by the coracoacromial arch (‘impingement’) [51,52]. Therefore, a rat model of supraspinatus tendon impingement was developed by wrapping an Achilles tendon allograft around the acromion, thereby decreasing the space between the acromial arch and the supraspinatus tendon [35]. While extrinsically-altered tendons demonstrated increased cellularity and decreased tissue organization, there were no statistically significant changes in cross-sectional area, maximum stress, or modulus [35,53]. However, when extrinsic factors were combined with the overuse treadmill running protocol as described earlier, statistically significant changes were observed for cross-sectional area, maximum stress, and modulus (Figure 4), and histological differences were also exaggerated [53,54]. Importantly, these mechanical and biological changes were significantly greater than the changes that resulted from overuse alone. These studies demonstrate that while extrinsic compression alone was not sufficient to produce significant changes in tendon properties, combinations of factors have the potential to create an even more detrimental tendinopathy in the supraspinatus tendon, supporting the concept that tendinopathy is often produced through a multifactorial process.

Another study developed a different model of subacromial impingement in the rat shoulder by transplanting bony plates onto the undersurface of the acromion [55]. One or two plates were implanted to decrease the space between the acromion and infraspinatus tendon. All experimental rats developed an infraspinatus tendon tear post-operatively, which always included the bursal side. Animals evaluated at a later time point had a higher incidence of large tears and the implantation of two plates resulted in a greater number of large tears as compared to one plate (Figure 4).

**Figure 4.** Cross-sectional area, maximum stress and modulus data showing that injury created by overuse plus extrinsic compression (OV/E) is greater than injuries created by extrinsic (E) or overuse (OV) alone; significant differences relative to control are indicated by an * above each pair of bars (reprinted from Soslowsky LJ, et al., Rotator cuff tendinosis in an animal model: Role of extrinsic and overuse factors. Ann Biomed Eng 2002;30(8):1057–1063, with permission from Springer Science and Business Media).
compared to animals receiving only one plate. Regions of tendon tissue adjacent to the ruptures exhibited a loss of normal collagen architecture and cells with abnormal nuclei, perhaps representing dead cells. In addition, groups of chondrocytes were observed in the experimental infraspinatus tendons, but not control, likely indicating fibrocartilaginous metaplasia in the regions of compressive loading. This model was shown to consistently induce infraspinatus tears, indicating that subacromial impingement may be involved in the pathogenesis of rotator cuff tears, particularly in the development of bursal side tears. In addition, the observed histological results suggest that some biologic changes consistent with tendinopathy developed in conjunction with, and perhaps prior to, tendon rupture in this model.

Chemically-induced Collagenase models

Animal models that employ an intrinsic method of degradation and inflammation are also widely used to study tendinopathy. Of these, the application of collagenase is the most widely used. It was first introduced [56] as a way to provoke an acceptable experimental injury without distressing the animals being studied. Briefly, it was found to induce a reproducible and consistent lesion that showed tendon degeneration accompanied by a classic inflammatory response [56,57]. Collagenase is now used in some research groups as a model to study both acute injury and tendinopathy. Studies in the horse, rabbit, and rat evaluating the flexor digitorum superficialis (FDS) tendon, deep digital flexor tendon (DDF), Achilles tendon, patellar tendon and supraspinatus tendon have been conducted. Conflicting results have been found but these may be due to differences in protocol. For example, the size of the lesion or degree of injury in the tendon is proportional to the amount of collagenase administered. In a research setting, however, this aspect of the model allows for tight control and potentially a dose response over altered parameters [56 – 66].

After collagenase injection, as would be expected, tendons generally displayed matrix disruption, extensive haemorrhage and fluid exudation. These results were seen by gross observation, a decrease in the echogenic intensity of ultrasound, and histologically. Gradually the symptoms were resolved and granulation tissue was deposited at the site of the wound. Improvement of tissue quality was demonstrated by a partial return of the tendon’s crimp pattern. However, crimp never fully returned to normal and the fibrils showed a loss of parallel orientation and a decrease in diameter. The cross-sectional area of the tendon as a whole was generally increased and also did not return to normal [35,56,57,67 – 73].

Type I collagen is the main component of the extracellular matrix of normal tendon and healing tendon; however, healing is characterized by higher than normal levels of type III collagen (Figure 5). Type III collagen is thought to contribute to a population of small fibrils, which may then lead to decreased mechanical properties. Both an increase in type III collagen and a decrease in fibril diameter were seen in collagenase injuries by immunohistochemistry, electron microscopy and northern blot

Figure 5. Collagen type III (A – G) and type I (H – N) and TGF-β1 (O – U) protein expression in normal tendon, and tendons sampled at 1, 2, 4, 8, and 24 weeks post-injection with collagenase. Samples were assessed by immunohistochemical reaction using the chromagen diaminobenzidine and hematoxylin counter-stain and demonstrate hypercellularity, increased collagen I and III, and the early peak of TGF-β1 as a result of collagenase injection. G, N, and U demonstrate representative sections exposed to non-immune serum as negative controls. Bar = 50 μm. (reprinted from Dahlgren LA, et al., Temporal expression of growth factors and matrix molecules in healing tendon lesions. J Orthop Res 2005;23(1):84 – 92, with permission from the John Wiley & Sons, Inc.).
analysis [56,61,62,67,74]. However, when hydroxyproline was measured, which is a reliable index for newly-formed collagen, a decrease in the injured tendon within 24 hours was evident. This decrease coincides with leukocyte infiltration [75]. Tendon crosslinks, a mark of more mature tendon and measured by pyridinoline content, were also shown to be significantly decreased after injury. In contrast, other studies showed that pyridinoline increased above normal [56,72,73]. Another important family of structural proteins in tendon are proteoglycans whose quantity is often approximated by measuring glycosaminoglycan (GAG) content. GAGs were temporally expressed and changes in specific GAG content were seen in collagenase models [76].

A notable change in the collagenase injury model was an increased cellularity that appeared as early as 24 hours post-injection and remained elevated for multiple months (Figure 5). The cellular response consisted of temporally expressed populations of leukocytes and fibroblasts [56,57,67–69,75,77–79]. Leukocytes were mainly present in the early stages of healing and could be seen around new vasculature. There was also a large population of metabolically active, immature, plump fibroblasts present throughout the lesion. Fibroblasts may have proliferated and migrated due to growth factors released from the leukocytes. Interestingly, DNA content, which is a measure indicative of cell quantity, either did not change or was decreased in some studies. The conflicting results may be due to different animal models and amount of collagenase administered. While it is difficult to observe this cellular response in human tendinopathy, it is seen in many injury models [35,56,57,60–62,67–73,76,77]. Growth factors are thought to have a significant effect on tendon healing and have thus been studied in collagenase-induced tendinopathy models. Specifically, insulin-like growth factor-1 (IGF-I) and its related binding proteins (IGFBP) were found to be temporally and differentially expressed [61,80]. In addition, IGFBP’s expression was shown to be associated with rising tissue levels of transforming growth factor-beta 1 (TGF-β1). TGF-β1 peaked during the inflammatory stages of tissue healing when there was also an up-regulation of matrix gene expression and cell proliferation (Figure 5) [61,69]. Another growth factor, platelet derived growth factor (PDGF), is a potent mitogen found in activated macrophages that induces chemotaxis and fibroblast proliferation. It is also thought to influence collagen and proteoglycan extracellular matrix concentrations through IGF-I and TGF-β1. Interestingly, PDGF-B expression was significantly decreased, and it was hypothesized that exogenous PDGF from platelet degranulation down-regulated the production of constitutive PDGF mRNA by tendon fibroblasts [81].

One of the largest problems in tendinopathy is a loss of function and therefore, function is an important aspect of modelling tendinopathy. Collagenase-induced injuries in the FDS tendon of horses have shown many alterations in the injured and in the contralateral leg. Changes were seen in clinical lameness, trotting speed, ground reaction forces, altered joint angles and gait efficiency (Figure 6) [82–84]. Functional changes were also observed when the DDF tendon and the suspensory ligament were injured [59,65,66]. Altered gait was also demonstrated in a rat model [70].

The mechanical strength of healing tendons is also a good measure of functionality. In a rabbit patellar tendon collagenase model no biomechanical differences were seen at a high strain rate. However, tests at a strain rate of 1 mm/min showed that the collagenase-injected tendons did not regain ultimate

![Figure 6. Mean vertical ground reaction forces during the stance phase for sound horses and horses that received a collagenase injection in one (lame) limb and no treatment in the contralateral (compensating) limb, demonstrating altered function as a result of collagenase injection (reprinted from Clayton HM, et al., Kinematics and ground reaction forces in horses with superficial digital flexor tendinitis. Am J Vet Res 2000;61(2):191–196, with permission from American Journal of Veterinary Research).](image)
The first non-collagenase agent that was used to induce tendinopathy was a mixture of cytokines and unknown agents [72]. No inflammatory cells were found, but there was a focal and diffuse increase in cellularity which later resolved. An increase in vascularity was also observed, as well as a decrease in ultimate load. The cytokine injection therefore modelled a mild and seemingly reversible tendon injury with no alterations in matrix histology. One limitation of the cytokines used in this study is that they were not well defined. Therefore, determining the exact mechanism of the injury is difficult.

An injection of carrageenan, a vegetable polysaccharide with no endogenous proteolytic activity, was used to study the contribution of leukocyte invasion to tendon damage [87]. An accumulation of neutrophils and macrophages was observed shortly after injection. In addition, MMP activity was increased while TIMP concentrations were decreased. No significant changes in collagen content or mechanics were found. This model induced a larger accumulation of macrophages than neutrophils, unlike collagenase studies that showed a larger population of neutrophils. This model is well suited to study the intrinsic role of inflammatory cells in inducing non-specific damage.

Corticosteroids are routinely used to treat injured tendon; however, there is evidence that the corticosteroids themselves could be inducing an injury. Healthy rat Achilles tendons were injected with corticosteroids and examined [88,89]. Findings included a thickened paratenon, visible adhesions, increased cellularity (including fibroblasts and monocytes) and increased vascularity. However, only about 20% of the injected animals showed symptoms in both the paratenon and tendon midsubstance. There was no damage to the matrix but an inflammatory reaction was instigated. These observations led the authors to conclude that corticosteroids are a good model to study the healing process of inflamed tendons and paratenon.

Lastly, prostaglandins have been used to induce tendinopathy because they are up-regulated in exercise [90,91] and in mechanically loaded fibroblasts in vitro [92]. In one study, prostaglandin 1 (PGE1) was injected around the Achilles tendon. The cross-sectional area of the tendon increased at all time points studied and histological changes were observed including rounded fibroblasts, and increased cellularity, vascularity and fibre disorganization [93]. When prostaglandin 2 (PGE2) was injected into the rat Achilles tendon, increased cellularity and fibril disorganization were evident along with decreased fibril diameter [94]. Interestingly, similar effects were shown after injection of pefloxacin, an antibacterial drug [1]. While prostaglandins have induced tendinopathy in experimental

### Table I. Flexor digitorum superficialis from horses 6 weeks after a 2000 U injection of collagenase or no injection. All horses were also injected intramuscularly with saline once a week for 6 weeks. Collagenase injected tendons demonstrate an increase in cross-sectional area, a similar load and therefore a decrease in stress at failure when compared to tendons without collagenase.

<table>
<thead>
<tr>
<th>Tendon group</th>
<th>Cross-sectional area (mm²)</th>
<th>Failure load (N)</th>
<th>Failure stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>115.8 ± 12.6</td>
<td>7553 ± 881</td>
<td>65.0 ± 4.1</td>
</tr>
<tr>
<td>Collagenase injected</td>
<td>371.8 ± 37.8</td>
<td>7265 ± 641</td>
<td>34.9 ± 4.7</td>
</tr>
</tbody>
</table>

animals, it has been speculated that they induce an up-regulation of collagenase. No study has yet evaluated the regulation of collagenases after the injection of prostaglandins. In addition, in studies that evaluated the amount of PGE2 in the Achilles tendon in subjects with tendinopathy, there were no significant changes [14].

Conclusion

Tendinopathy is a common occurrence that afflicts both young and old people alike. While several important studies have evaluated the aetiology, pathogenesis, and treatment of this condition, further study is needed. As shown in this review, animal models provide a critical approach to fully evaluate tissue on different organizational levels and stages of disease. A variety of different animal models have been developed to model the human condition of tendinopathy. Mechanically-induced models generally incite tendinopathy using repeated applications of a sub-traumatic level stimulus. While these mechanical injuries can be labour intensive and time consuming to develop, they are beneficial since they induce injury through repetitive mechanical loading, which is generally believed to be the natural development of human tendinopathy. In contrast, chemically-induced models, which incite tendinopathy through the introduction of a biological or chemical agent, are relatively non-invasive, easy to perform, reproducible and well validated. However, since the most studied model, collagenase-induced tendinopathy, disrupts tendon tissue by digesting collagen fibres rather than by inducing mechanical damage, the aetiology of disease in these models is likely to be different from human tendinopathy. While this model incites a significant inflammatory reaction which is not seen in human tendinopathy, it is possible that human tendinopathy has an inflammatory phase that is simply difficult to observe and short-lived. Chemically-induced models are beneficial by allowing for the study of the interplay among inflammatory cells, mechanical loading and tissue healing.

Other factors to consider when evaluating models for potential use are cost and efficiency of use for a particular research question and/or study design, which may make a specific model effective or prohibitive in attempting to address and answer study hypotheses. While specific issues vary with each particular model, in general mechanically-induced models are more expensive to develop. Since injury is created over time, long periods of animal housing, care and significant personnel time are often required. In addition, instrumentation or equipment is often needed to apply the injury stimulus. In contrast, chemically-induced models are generally less expensive since injury can be applied immediately, usually involves a single application of the stimulus, and requires few supplies. Another factor that affects cost is the size of the animal species used. Large animals are expensive to purchase, house and feed, while small animal models have the advantage of being available consistently in large quantities at reasonable costs. Small animal models can be used to perform broad studies and address many factors in various experimental groups simultaneously. However, large animal models may be necessary for certain modes of injury application and are often required by regulatory agencies prior to development of clinical trials in humans. While these issues should not be the driving factor in determining which animal model to use, these considerations may be helpful when more than one model could successfully address study aims.

Due to the complex nature of tendon injuries, further work is needed to fully characterize and understand these models. As appropriate models are developed and evaluated, a greater understanding of human tendinopathy will be attained, leading to better prevention and treatment of tendinopathy.

References


