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Animal Models of Tendinopathy Induced by Chemicals

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Abstract

Tendinopathy is a common disease that afflicts a wide range of people irrespective of age and gender. The underlying pathogenesis is still poorly understood. Since it is impossible to directly conduct experiments on humans, animal models of tendinopathy are essential not only to study its developmental mechanisms, but also to devise new treatment options for tendinopathy. Chemically-induced models are usually low-cost, reproducible, less labor-intensive and easy to perform. Chemicals that are currently being used to produce tendinopathy in animals include collagenase, cytokines, transforming growth factor-β1 (TGF-β1), fluoroquinolone, kartogenin, prostaglandin, statin, carrageenan and elastase. This paper discusses the development and use of animal models induced by chemicals.

Keywords: Tendon; Tendinopathy; Animal model; Chemical-induced; Collagenase

Introduction

Tendinopathy, a disease of the musculoskeletal system which is prevalent in the general population and especially in athletes, is characterized by activity-related chronic pain, focal tendon tenderness, tendon swelling and intratendinous imaging changes. The etiology of the disease is not completely clear. Mechanical overloading of tendons is one of the commonly agreed factors. Other factors including age, gender, body weight, gene polymorphisms, and anatomical and biomechanical variations are thought to be involved in the etiology of tendinopathy [1]. Tendinopathy is becoming one of the most common non-fatal disease of the 21st century, and an important cause of work disability and loss of quality of life [2]. If not adequately treated, tendinopathy may lead to complete tendon rupture, which often requires surgical repair. Although some progress has been made and various treatments have been applied to treat tendinopathy in recent years, we still know little about the underlying pathogenesis of tendinopathy. One of the principal reasons is the limited availability of specimens. While tissue can be obtained surgically, the tissue obtained from patients undergoing surgical procedures is generally already well developed in terms of histopathology. Additionally it is rarely possible to obtain developing specimens from patients because their condition is usually not sufficiently severe to warrant surgical intervention. Hence, a validated animal model is essential to enable in-depth studies on the etiology and pathogenic mechanism of tendinopathy, to find out how the disease occurs and develops, and to seek new treatment for it.

Currently, there are many ways to establish animal models of tendinopathy, and most of them can be categorized into two groups. One is mechanical overloading which is considered to be the most common extrinsic factor causing tendinopathy [3-5]. The other model group, which relies on intrinsic factors, involves the introduction of chemicals into normal animal tendons [6-8]. This paper discusses the development and use of animal models induced by chemicals, highlights potential outcome measures that may be used in animal tendon research, and reviews current animal models of tendinopathy induced by chemicals.

Materials and Methods

All literatures were retrieved from PubMed database. The keywords "tendinopathy," "tendinosis" "tendinitis" and "animal model" were used for searching the literature published before September 2020. After screening the title, abstract and full text of each article, duplicate and irrelevant articles were removed, and 73 articles were finally included in this review. The flow chart of searched results presented in Figure 1.

Assessment criteria of tendinopathy animal models

To determine if an animal model is valid, there should be consensus criteria. Seeing that our knowledge about tendinopathy is limited, a standard criterion of tendinopathic animal models is not yet published. But there are some crucial features from human tendinopathy samples that animal models should consistently replicate in order to be valid. Histopathologically, the alteration in human samples include loss of matrix organization or collagen arrangement, excessive proliferation of tenocytes and changes in tenocyte morphology (hypercellularity), extensive neovascularization and vascular ingrowth (hypervascularity), increase in non-collagenous matrix such as glycosaminoglycans (GAG) [2,9-12]. In regard to mechanics, altered biomechanical properties should be apparent [13]. Also, changed molecular expression, such as matrix metalloproteinases (MMPs) and collagens, should be taken into account [10,14]. Animal models should replicate the above histopathological, mechanical and genetic features of tendinopathy

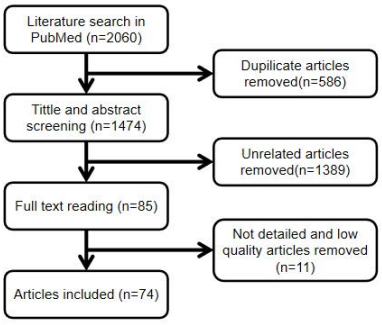

Figure 1: The flow chart of literature search and screening.

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in humans to be considered valid. If there are new findings in human tendinopathy pathology, animal model criteria should be updated accordingly.

Current chemicals to produce animal models of tendinopathy

Collagenase: Among the chemicals to produce animal models of tendinopathy, collagenase is the earliest and most widely used15. It was initially pioneered by Silver et al to study tendinitis by mimicing the intrinsic condition of tendon rupture. Briefly, it was found to induce a reproducible lesion consistent with spontaneous tendon injury which showed tendon degeneration accompanied by a classic inflammatory response which exist about one week [15,16]. Collagenase is currently being used by many research teams to establish tendinopathy models in animals including horse, sheep, rabbit and rat, in various anatomic locations such as the superficial digital flexor tendon (SDFT), deep digital flexor tendon(DDFT), Achilles tendon, patellar tendon and rotator cuff [17-23].

Collagenase is usually applied by intratendinous injection (Table 1). After injection, the tendon exhibits collagen matrix and fiber disorganization, increase in rounded cell density, and s marked increase in vascularity [6,22,24,25]. Altered biomechanical properties including larger cross-sectional area, decreased load to failure, lower stiffness, etc, have all been observed [25-28] (Table 1). These characteristics are similar to those observed in human samples. And the severity of collagenase induced injury seems to be dose-related [6].

In human, collagen type I is the major collagen type in healthy tendon, but when matrix degeneration resulting from tendinopathy occurs, a decrease in collagen type I and an increase in collagen type III occurs [29,30]. Findings from Liu et al in their collagenase model of rats displayed the same results as previously described [31]. In their research, they also found sustained or increased expression in decorin, biglycan, fibromodulin and aggrecan which are consistent with clinical samples [11,32,33] and increased expression in substance P(SP) and calcitonin gene-related peptide(CGRP) which positively correlates with activity-related tendon pain. Dahlgren and colleagues reported type III collagen expression is initially increased in endotenon and subsequently in the parenchyma of healing tendon [34].

Matrix metalloproteinases are thought to participate in the pathogenesis of tendinopathy. MMPs are members of a family of enzymes that can break down proteins such as collagen. It makes tendon more susceptible to microdamage, and further accelerate lesions. Numerous researchers reported a substantial increase in the expression of MMPs (MMP-1,MMP-3,MMP-9,MMP-13), and a decrease in the expression of its counterpart inhibitor, i.e., tissue inhibitor of metalloproteinases (TIMP), in the collagenase model (Table 2). Injury treatments including piperine, low level laser therapy, photobiomodulation therapy, and platelet-rich plasma were performed in these experiments and showed inhibitory effects on MMPs [19,35-40].

In conclusion, tendinopathy induced by collagenase exhibit many major qualities seen in clinical cases. It can be considered as an efficient and valid model of tendinopathy. However, it should be noted that drawbacks also exist. There is an acute inflammatory reaction after injection which is not seen in human. Also, a chronic healing response caused after collagenase injection is incompatible with clinical cases; for humans, the healing process is usually impaired [16].

Cytokines: Stone and colleagues wished to produce a model that better emulate the reversible lesions that represent the majority of the painful tendons seen in clinical practice. They injected cytokine preparation into the rabbit patellar tendon and compared the results with the collagenase-injection model (Table 1). The cytokine preparation is a mixture of interleukin-lα (IL- lα), TGF-β, basic fibroblast growth factor, and other unidentificd growth factors. At 4 weeks, tendons injected with the cytokine had increased cellularity, and a normal-appearing collagen matrix. No inflammatory cells were seen. Slightly increased vascularity in the tendon was noted. While there was a significant decrease in the ultimate load at 16 weeks, there was no change in tendon cross-sectional area (Table 2). No significant change in the collagen content and crosslinking density were seen. No matrix damage or evidence of collagen degradation was produced. There were only mild injuries induced by cytokines compared to collagenase, Taken together, there is a lack of evidence that cytokines injections produce a valid model of tendinopathy [41].

TGF-β1: In recent years, TGF-β1 has been used to establish a tendinopathy model in mice [8,42,43]. The reason for the use of TGF-β1 is that TGF-β1 has been demonstrated to stimulate both chondrogenesis in numerous tissue and cell culture models, and is a critical biological factor translating mechanical overuse injury of tendon cells, into a biological response. Male mice were injected with 100ng TGF-β1 in the mid portion of the Achilles tendon (Table 1), and the mice were killed at 48H, 2W and 4W thereafter. The injected tendons showed a robust increase in collagen III and ADAMTS5 at 48h after injection. Accumulation of GAG, as well as an increase in chondrocyte-like cells, and collagen disorganization, was observed at 2 and 4 weeks. Significant reductions in stiffness, maximum stress, tensile modulus, and an increase in cross-sectional area were seen at 2 weeks8. These results are consistent with those seen in human. But another study reported that after injection, alterations included hypercellularity, collagen disorganization, and chondroid deposits at 14 days, which largely dissipated by 28 days, suggesting a feeble pathological continuity [43] (Table 2).

In conclusion, the injection of TGF-β1 can induce pathological

Table 1: Operate method of chemicals to make animal model.

Chemicals	Operate Method	Species	Anatomical Location
Collagenase	Ultrasound guided local injection or direct local injection	Rat, mouse, rabbit, horse, sheep,	Achilles tendon, patella tendon, deep or superficial digital flexor tendon
Cytokine	Direct local injection	Rabbit	Patellar tendon
TGF-β1	Direct local injection	Mouse,	Achilles tendon
Fluoroquinolones	Gavage administration	Rat, dog	Achilles tendon
KGN	Surgical implantation	Rat	Achilles tendon
PG	Direct local injection	Rat, rabbit	Achilles tendon, Patellar tendon
Statin	Gavage administration	Rat	Achilles tendon
Carrageen	Direct local injection	Rat	Achilles tendon, patellar tendon, footpad
Elastase	Ultrasound guided local injection	Rat	Achilles tendon
Abbreviations: TGF-β1, transforming growth factor-β1; KGN, kartogenin; PG, prostaglandin			

Table 2: Current chemicals to produce animal models of tendinopathy.

Changes induced by chemicals				
Chemicals	**Histopathological**	**Mechanical**	**Biochemical**	**Conclusion**
Collagenase	1.fiber disorganization 2.hypervascularity 3.hypercellularity	1.increased cross-sectional area 2.decreased load to failure 3.lower stiffness	1.decreased Coland increased Col content 2.increased ecpression in decorin, biglycan, fibromodulin, aggrecan, SP, CGRP, MMPs	1.The most widely used modeling method. 2.Reproduced many major qualities seen in clinical cases. 3.Acute inflammation and chronic healing response caused by collagenase is not seen in clinical cases.
Cytokines	1.hypercellularity 2.slightly increased vascularity	1. significant decrease in the ultimate load at 16 weeks	absent	1.Less valid ,because the model is lack of enough reproduced symptoms of human tendinopathy.
TGF-β1	1.Collagen disorganization 2. hypercellularity 3.chondroid deposits	1.significant reduction in stiffness, maximum stress, tensile modulos 2.increased cross-sectional area	1.accumulation of GAG 2.increase in Col and ADAMTS5	1.Reproduced many major qualities seen in clinical cases. 2.Unstable pathological changes and short of long-term status of the model. 3.A useful model for acute tendinopathy
Fluoroquinolone	1.fiber disorganization	absent	1.decrease in Col , elastin, fibronectin, β1-integrin	1.Reproduced some features of tendinopathy. 2.Not valid for general tendinopathy research.
KGN	1.Collagen disorganization 2.hypervascularity 3.hypercellularity	absent	1.proteoglycan accumulation 2.up-regulated aggrecan, Col , sox-9 in TSCs	1.Reproduced many major qualities seen in clinical cases. 2.Short of long-term status of the model. 3. Lack of mechanical evidence.
PG	1.hypercellularity 2.tendon disorganization and degeneration	absent	absent	1.Reproduced good histopathological features of tendinopathy but evidence in other aspects are Insufficient.
Statin	1.fiber disorganization	1.decreased maximum stress and load	1.increase in GAG 2.increase in MMPs expression 3.decrease in Col	1.Reproduced some features of tendinopathy. 2.Not valid for general tendinopathy research.
Carrageen	1.matrix degeneration 2.cell infiltration 3.Collagen disorganization 4.hypercellularity 5.angiogenesis	1.decreased ultimate failure load	1.presence of MMP9 2.degradation of non-collagenous proteins and GAG	1.Reproduced some major features of tendinopathy. 2.Distinct infiltration of inflammatory cells caused by carrageen is incompatible with clinical cases.
Elastin	1.hypervascularity 2.hypercellularity 3.Collagen fiber disorganization and fragmentation	1.increased tendon thickness 2.decreased weight-bearing	1.decreased Col expression 2.increased Col expression	1.Reproduced many major qualities seen in clinical cases. 2.Need more literature in future to verify its validity.

Abbreviations: Col , collagen type ; Col, collagen type ; Col , collagen type; GAG, glycosaminoglycan; SP, substance P; CGRP, calcitonin gene-related peptide; MMPs, matrix metalloproteinases; TSCs, tendon stem cells.

changes in mice which similar to those seen in human tendinopathy. But deficiencies also exist. First, the long-term status of the model is not available because of the short duration of induced changes which only last for 4 weeks. Second, the progression of pathological changes is unstable. For the above reasons, this model may be useful for studies on acute tendinopathy, it does not provide an opportunity to conduct studies on chronic tendinopathy. Further efforts should be designed to prolong the observed changes to establish a more human injury simulating model.

Fluoroquinolone: Fluoroquinolone is an antibiotics which is widely used in the clinic. There have been reports that fluoroquinolones can cause tendon lesions including pain, swelling and even rupture [44-46]. The clinical observations suggest that fluoroquinolone symptoms related to tendinopathy, and thus fluoroquinolone is used to produce tendinopathy in animals (Table 1). Kashida and Kaot [47] compared the toxic potentials of 10 fluoroquinolones on the Achilles tendon in juvenile rats. Ten fluoroquinolones were orally administered, and animals were sacrificed 24 hours after administration. Results showed edema and increased mononuclear cells in the tendon sheath. Among 10 fluoroquinolones, fleroxacin and pefloxacin were the most toxic, while norfloxacin, ciprofloxacin and tosufloxacin showed no toxicity. Shakibaei and colleagues further examined the effects of ciprofloxacin and fleroxacin. After orally administering ciprofloxacin to dogs for 5 days, there were decreases in collagen type I, elastin, fibronectin and β1 integrin content in the Achilles tendon [48]. Detachment of tenocytes from the extracellular matrix (ECM), a decrease in fibril diameter and an increase in fibril separation in Achilles tendon were reported 4 weeks after a single dose of fleroxacin in rats [49] (Table 2). Although fluoroquinolones reproduced some features of tendinopathy, this model lacks of universality. Fluoroquinolones are generally not involved in most cases of tendinopathy, so this model is quite fluoroquinolones-specific. Meanwhile, not every patient taking fluoroquinolones shows the symptom of tendinopathy. The use of fluoroquinolones to establish animal model of tendinopathy is thereby questioned.

Kartogenin (KGN): Chondrocyte-like cells have been observed in the degenerated tendon regions in tendinopathy patients [50]. Kartogenin is a small heterocyclic compound that can stimulate endogenous stem/progenitor cells such as mesenchymal stem cells to differentiate into chondrocytes in mice [51]. In order to create an animal model with a more relevant injury location, Yuan et al implanted fine beads of a bio-compound called kartogenin into rat tendons [52] (Table 1). After 5 weeks of normal cage feeding, rats were sacrificed. Gross appearance showed thickening of the paratenon tissues. Hypercellularity, hypervascularity, collagen disorganization, anti-CD31 antibody and extensive amounts of proteoglycans were revealed in stained tendon sections. These findings indicate that

KGN induces localized chondrogenesis with neo-vascularization in rat Achilles tendons. They also performed in vitro experiments to understand the cellular mechanism by which KGN induces the formation of cartilage-like tissues in vivo. Results showed that KGN up-regulated three chondrocyte specific genes, aggrecan, collagen type II and Sox-9 in tendon stem cells(TSCs) treated with KGN in vitro [52] (Table 2). Briefly, certain features of degenerative tendinopathy frequently observed in clinics have been captured by KGN-induced in an animal tendinopathy model. These findings suggest KGN has the potential to be a useful model of tendinopathy. Disadvantage is that the implantation procedure is a little more complex than injection and gavage. And further studies should focus on the long-term alterations of KGN model.

Prostaglandin (PG): Prostaglandin has been used to induce tendinopathy, it is based on up-regulated production of prostaglandin-E2 (PGE2) by human tendon fibroblasts under mechanical stimulation in vitro [53] and increased PGE2 expression after exercise in vivo [54]. PGE2 was injected into the rabbit patellar tendon once a week for 4 weeks (Table 1). Following treatment, hypercellularity, abnormal tissue architecture, tendon disorganization and degeneration were evident, coupled with decreased fibril diameter (Table 2). Interestingly, despite PGE2 being a known inflammatory mediator, there were no inflammatory cells in the tendon 1 week after repeated PGE2 injection. This suggests that degeneration may be the principal effect of PGE2 instead of inflammation [55]. PEG1 was also applied to the peritendinous Achilles tendon of rats. Acute inflammation was manifested 1 week after injection, followed by weeks of degeneration characterized by increased vascularity, cellularity and fiber disorganization [56]. The limitation of PGEs is the lack of long-term effects of prostaglandin injections. Evidence in biomechanics and molecular level processes has not been reported.

Statin: Statins are widely prescribed medications used for the treatment of hyperlipidemia. Tendinitis and tendon ruptures have been observed in frequent user of stains. Effected tendons include the distal biceps tendon, the quadriceps tendon, the patellar tendon and the Achilles tendons, the latter of which is the most commonly affected one [57-60]. Statins, therefore, may be involved in the etiology of tendinopathy and may be used as agents to produce tendinopathy in animals (Table 1). Statins may change the ECM components in the tendon, with increases in GAGs and decrease in collagen I accompanied by active expression of MMPs [61]. The use of atorvastatin and simvastatin in a rat model demonstrated reduced epitenon thickness, fiber disorganization, increased amount of ED1+ macrophages and impaired biomechanical strength in the Achilles tendon [62] (Table 2). Other research also reported foci of dystrophic calcification in Achilles tendon with improved biomechanica properties of the tibias simultaneously [63]. Although statins may induce tendinopathy in human, they are generally not involved in most cases of tendinopathy and neither do they induce tendinopathy in every patient. It may be useful to explore the side-effect of statins on tendons, but the valid of statin-indued tendinopathy animal model is doubtable.

Carrageenan: Carrageenan is a polysaccharide extracted from the cell wall of Rhodophyta algae. It is widely used to induce inflammation in vivo [64,65]. It has long been debated whether inflammation takes part in the underlying pathogenesis of tendinopathy and carrageenan has been used to study the effects of inflammation on tendons (Table 1). Tillander et al. revealed that repeated subacromial injection of carrageenan resulted in bursitis featured by degenerative matrix, macrophage infiltration and bone and fibrocartilaginous metaplasia in the rat supraspinatus tendon [66]. Vieira et al. injected carrageenan into the paratenon of the deep digital flexor tendon to study the effect of inflammatory tissue adjacent to tendon. Although the injury was not directly introduced into tendon, remarkable results include presence of MMP-9, degradation of non-collagenous proteins and GAG, cellular infiltrate and less organized collagen bundles were detected in the tendon [67,68]. Experiments conducted by Vieira et al. were finished within 24 hours, which means their findings were instant consequences of carrageenan. Hypercellularity, fiber disorganization, angiogenesis, cell Infiltration, nuclear rounding and decreased ultimate failure load were illustrated in rat tendon after carrageenan injection for weeks [7,69,70] (Table 2). It should note that both instant and sustained use of carrageenan gives rise to a distinct infiltration of inflammatory cells which is usually non-existent in clinically diseased specimens. This makes carrageenan-induced tendinopathy less credible. However, because it was difficult to obtain early clinical samples, the presence of inflammation at the early stages or before the onset of symptoms in human tendinopathy cannot therefore be excluded. This model provides a possible way to study the intrinsic role of inflammatory cells in tendinopathy.

Elastase: Elastase is an elastin degarding enzyme. The degradation products of elastin stimulate the release of proteolytic enzymes-MMPs, which would further lead to the destruction of matrix and structural components of tendon [71,72]. Because elastase may affect tendon components, Wu et al. investigated the role of elastase on tendinopathy by peritendinous injections of elastase into rats [73] (Table 1). On the one hand, they examined the expression of elastase in tendons of patients with tendinopathy, and concluded that elastase expressions may be related to the severity of a tendon injury. On the other hand, experiment on rat model displayed positive results. Increased tendon thickness and decreased weight-bearing of tendon were observed after elastase injection on the Achilles tendons of rats. Histological changes included hypervascularity, hypercellularity, collagen fiber disorganization and fragmentation were found by staining. Decreased collagen type I expression and increased collagen type III expression were examined by western blot (Table 2). These studies suggested that elastase plays a critical role in the pathogenesis of chronic tendinopathy. Limitations included dosage of elastase, grading methods of tendinopathy and the lack of end-stage tendinopathy syndrome were noted by the author. Based on the findings, we can conclude that elastase may provide a potential animal model for tendinopathy, but additional verification is needed.

Conclusion

Tendinopathy is a common disease that torments a large percentage of the population. As experimentation on humans to investigate the etiology, pathogenesis and evaluate new treatments is impossible, the establishment of a valid animal model is therefore indispensable. In this paper, several methods for chemically inducing tendinopathy in animals are reviewed. Chemically-induced models are usually low-cost, reproducible, less labor-intensive and easy to perform compared to mechanically-induced models. Chemicals mimic the pathological features, not the known first cause of tendinopathy which is believed to be the over-loading of the tendon. However, we cannot always identify what is the first cause of a disease, and tendinopathy is clearly a multifactorial one, and using one single model to represent all aspect of tendinopathy is unrealistic. Given the limited circumstances presently, we can only try our best to simulate the natural process of disease occurrence. Combining various factors, for example applying chemical and mechanical factors at the same time, to create animal model may provide us with a model closer to natural in future. Parameters been selected are also essential to model assessment, future study should

add better relevant parameters, such as pain assessment, in assessment criteria.

Conflict of Interests

The authors declare that they have no conflict of interests.

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