Seminars in Arthritis and Rheumatism 43 (2014) 570–576

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

The risks and benefits of glucocorticoid treatment for tendinopathy: A systematic review of the effects of local glucocorticoid on tendon

Benjamin John Floyd Dean, MRCS*, Emilie Lostis, BSc, Thomas Oakley, BM, BSc, Ines Rombach, MSc, Mark E. Morrey, MD, Andrew J. Carr, FRCS

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Botnar Research Centre, Institute of Musculoskeletal Sciences, Nuffield Orthopaedic Centre, Windmill Rd, Oxford OX3 7LD, UK

ARTICLE INFO

Keywords:
Glucocorticoid
Tendon
Tenocyte
Steroid
Fibroblast

ABSTRACT

Objective: Our primary objective was to summarise the known effects of locally administered glucocorticoid on tendon tissue and tendon cells.
Methods: We conducted a systematic review of the scientific literature using the PRISMA and Cochrane guidelines of the Medline database using specific search criteria. The search yielded 50 articles, which consisted of 13 human studies, 36 animal studies and one combined human/animal study.
Results: Histologically, there was a loss of collagen organisation (6 studies) and an increase in collagen necrosis (3 studies). The proliferation (8 studies) and viability (9 studies) of fibroblasts was reduced. Collagen synthesis was decreased in 17 studies. An increased inflammatory cell infiltrate was shown in 4 studies. Increased cellular toxicity was demonstrated by 3 studies.

The mechanical properties of tendon were investigated by 18 studies. Descriptively, 6 of these studies showed a decrease in mechanical properties, 3 showed an increase, while the remaining 9 showed no significant change. A meta-analysis of the mechanical data revealed a significant deterioration in mechanical properties, with an overall effect size of −0.67 (95% CI = 0.01 to −1.33) (data from 9 studies).
Conclusions: Overall it is clear that the local administration of glucocorticoid has significant negative effects on tendon cells *in vitro*, including reduced cell viability, cell proliferation and collagen synthesis. There is increased collagen disorganisation and necrosis as shown by *in vivo* studies. The mechanical properties of tendon are also significantly reduced. This review supports the emerging clinical evidence that shows significant long-term harms to tendon tissue and cells associated with glucocorticoid injections.

Introduction

In September 1948 at the Mayo clinic, cortisone was injected into a patient for the first time in the treatment of rheumatoid arthritis to dramatic effect [1]. The 1950 Nobel Prize in Physiology or Medicine was awarded jointly to Edward Calvin Kendall, Tadeus Reichstein and Philip Showalter Hench directly relating to this work "*for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects*." The use of glucocorticoid in the treatment of painful musculoskeletal disease has since proliferated to the point that now in the UK over 500,000 intra-articular glucocorticoid injections (GCIs) are administered per year in the primary care setting [2]. GCIs are used to relieve pain and/or inflammation in a wide variety of musculoskeletal disorders including osteoarthritis, inflammatory arthritis, tenosynovitis, tendinopathy and degenerative spine disease. The evidence regarding the clinical efficacy of GCIs is conflicting but broadly shows some short-term benefits in terms of pain relief [3–6]. For example, in the treatment of shoulder pain, trials have shown only short-term benefits with no significant long-term gains [6–8]. Emerging high-quality evidence also points to poorer long-term outcomes associated with GCIs in the treatment of tendinopathy [9].

GCIs are frequently applied in close proximity to tendons with common examples including the rotator cuff, the flexor and extensor tendon origins around the elbow, the gluteus medius, the Achilles and the patellar tendons, the flexor tendons in the hand (i.e., trigger finger) and the extensor tendons around the

The authors of this work are funded by the Musculoskeletal Biomedical Research Unit of the National Institute for Health Research (B.D., M.M., E.L., T.O. and A.C.), the Jean Shanks Foundation (B.D.) and Orthopaedic Research UK (B.D.). The funding sources had no role in the study design, collection, analysis and interpretation of data; in the writing of the article; and in the decision to submit the manuscript for publication.

* Corresponding author at: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Botnar Research Centre, Institute of Musculoskeletal Sciences, Nuffield Orthopaedic Centre, Windmill Rd, Oxford OX3 7LD, UK.
E-mail address: benjamin.dean@ndorms.ox.ac.uk (B.J.F. Dean).

0049-0172/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.semarthrit.2013.08.006

wrist (i.e., De Quervain's tenosynovitis). It has been recurrently postulated that there is an increased risk of tendon rupture associated with GCI [10] but no high-quality evidence exists to adequately confirm or refute this hypothesis [11,12]. It is important to remember that GCI is often used in the context of an abnormal diseased tendon in which the risk of rupture is already increased. However, there is strong evidence that oral corticosteroids are associated with a higher risk of tendon rupture [13], and an increased spinal fracture risk associated with epidural GCIs has also recently been reported [14]. The mechanisms of action of glucocorticoids are multiple, highly complex and incompletely understood [15,16]. One important pathway involves the activation of specific cytoplasmic glucocorticoid receptors, which then migrate to the cell nucleus to affect gene transcription. Generally, glucocorticoids are thought to be anti-inflammatory, but the reality may not be so simple [17].

The tendon changes that occur in painful human tendinopathy are generally considered to be consistent with a failed healing response [18,19]. Normal tendon healing occurs with sequential inflammatory, proliferative and remodelling phases [20]. Fibroblast proliferation, angiogenesis and nerve ingrowth are all important in the healing process [21,22]. Tendinopathy is characterised by abnormal tenocyte morphology and disorganised collagen architecture [19]. Although the presence of inflammation in tendinopathy has been proposed by some authors [23], few studies have shown the presence of a "classical" inflammatory process involving the inward migration of inflammatory cells driven by inflammatory mediators [24]. Therefore, the logic of using GCIs in the treatment of a tendinopathy is not convincing.

In this context, the purpose of this review was to determine the effects of local GCI on both tendon tissue and tendon cells. We aimed to describe and summarise the histological, molecular and mechanical changes.

Methods

Search strategies

This systematic review used the PRISMA-Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane handbook as guidelines in the development of the study protocol and the report of the current study [25,26]. The inclusion criteria and methods of analysis were specified in advance and documented in a protocol.

Studies were identified using the Medline electronic database. No limit was placed on the year of data entry, but in practice, there were no results prior to 1956. The search was undertaken in June 2013. The following search terms were used: steroid OR corticosteroid OR glucocorticoid AND tendon OR rotator cuff OR Achilles OR tendin* OR tenocyte.

Additional studies were located by searching papers referenced in listed articles. The studies identified by the searches were combined, and duplicates were excluded. The abstracts were initially screened before analysis of the selected full-text articles. Full inclusion/exclusion criteria are detailed in Appendix 1. Studies had to relate to the use of local glucocorticoid on tendon tissue or tendon cells. Review articles and case studies were excluded. Papers pertaining to steroids other than glucocorticoids, such as anabolic steroids, were excluded. Those articles addressing steroid use other than for a peri-tendinous or tendinous injection, such as intra-articular steroid injection, were excluded. Studies using systemic steroid as opposed to injected corticosteroid were excluded. Any study without results relating to histological, cellular, molecular or mechanical tissue changes was excluded. If a study could not be obtained in English, it was excluded.

The search, selection of studies and data analysis were performed independently by 2 individuals (T.O. and BD for the articles on humans and E.L. and B.D. for the articles on animals). Agreement on inclusion was achieved after review of the full-text articles and a joint decision by both individuals based on the inclusion/exclusion criteria. The data were then extracted using a spreadsheet designed by 2 authors (B.D. and E.L.), this included data relating to study heterogeneity and methodological quality. The data extracted included study subject characteristics, glucocorticoid used, source of cultured cells and cells used method of tissue analysis, control group, results and statistical methods. Methodological quality was assessed using an 8-point scoring system (Appendix 2) based on the method used by Hegedus et al. [27].

Study selection

The search strategy yielded 4424 results (Fig. 1). After the exclusion of duplicates and review articles, there were 1996 articles. Screening the articles revealed 40 articles on humans and 38 articles on animals that met the criteria based on their abstracts. Further assessment of eligibility, based on full-text articles, led to the exclusion of 28 of these 78 papers. The reasons for the exclusion of these 28 papers were as follows: no control group [6], reviews [12], systemic glucocorticoid therapy [6] and not related to tendon [4]. This left 50 articles meeting our inclusion criteria, and they are summarised in Appendix 3.

Study characteristics

Of the 50 included articles, 36 related to animal studies, 13 to human studies and 1 to a study that was on both animals and humans. Of the 36 animal studies, 25 were *in vivo* and 11 *in vitro*; while of the 13 human studies, 12 were *in vitro*, 1 was *in vivo*, and 1 study was both *in vivo* and *in vitro*. The 1 combined human and animal study was *in vitro*. The most common animal used was rat (19 studies), followed by rabbit (9 studies), chick embryo (5 studies), dog (2 studies), cow (1 study) and multiple animals (1 study). The 25 *in vivo* animal studies used Achilles tendon

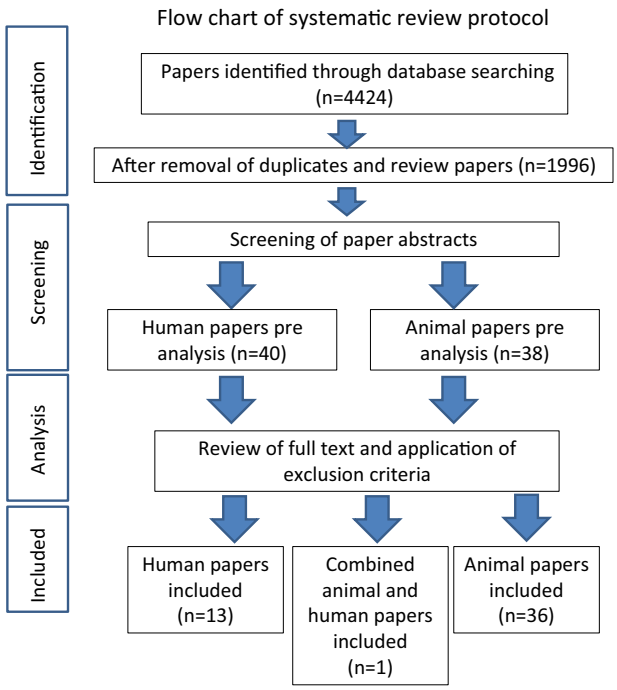

Fig. 1. Flow chart of systematic review protocol.