Doxycycline improves tendon and cartilage pathologies in preclinical studies: current concepts

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ABSTRACT

Matrix metalloproteinases (MMPs) are enzymes that are elevated during states of inflammation and have specifically been linked to cartilage, tendon and bone pathologies. Concentrations of these enzymes fluctuate naturally with various injury states, and these enzymes have been shown to be directly inhibited by doxycycline. Historically, doxycycline has been used exclusively for its antimicrobial properties, but recent studies have investigated the anti-inflammatory properties of doxycycline and its effects on musculoskeletal pathologies. This study sought to describe the current use of doxycycline for its MMP inhibitory properties in the setting of musculoskeletal pathologies. During preclinical studies, improved healing properties were noted acutely in tendon injuries following surgical repair and chronically in cartilage injuries, demonstrating decreased rates of joint space narrowing and improved cartilage quality. There is only one known clinical trial that has examined doxycycline use, and it reported that doxycycline can decrease the rate of joint space narrowing in patients with osteoarthritis. Furthermore, doxycycline was well tolerated with minimal side effects reported in both animal and human studies. While it can be reasonably inferred that the positive effects of doxycycline are related to its ability to inhibit MMP activity, further clinical research is warranted to investigate the use of doxycycline in orthopaedic and musculoskeletal pathologies. Level of Evidence: Current Concepts, Level IV.

Current concepts

- Doxycycline inhibits matrix metalloproteinases.
- Matrix metalloproteinases are elevated in cartilage, tendon and ligament pathologies.
- Doxycycline use has demonstrated improved healing in preclinical studies for acute tendon pathologies.
- Doxycycline use has demonstrated improved cartilage healing and deceleration of joint space narrowing in preclinical trials.
- Few adverse effects have been reported with the use of doxycycline in clinical and preclinical studies.

Future perspectives

- Future clinical trials examining the effectiveness of doxycycline following acute repair of tendon ruptures, specifically Achilles tendon ruptures, are warranted. Studies should also consider presurgical doxycycline dosing and its impact on earlier return to activity.
- Further clinical trials targeting the application of chronic doxycycline administration in osteoarthritis should be considered. While few side effects were reported in the only known clinical trial, future studies should focus on localising doxycycline therapy to the affected area.
- Preclinical studies examining the effects of doxycycline on both bony and ligamentous pathologies are warranted, specifically in acute anterior cruciate ligament reconstructions using bone-tendon-bone autografts and bone grafting procedures. In these studies, early reincorporation and pain should be the primary focus.

INTRODUCTION

Matrix metalloproteinases (MMPs) are the primary enzymes responsible for the degradation of collagens and the basement membrane of the extracellular matrix (ECM).[1–4] MMPs are clinically significant because they play a primary role in angiogenesis, morphogenesis and tissue repair. In orthopaedics, these proteinases are upregulated in inflammatory conditions such as tendinopathies, chondromalacia and also in prolonged immobilisation following anterior cruciate ligament (ACL) reconstruction.[3–5] A balance of MMP activity is essential, because disproportionately elevated MMP activity can result in excessive tissue breakdown affecting tissue integrity, while insufficient MMP activity can negatively affect tissue remodelling and repair.[4] Naturally occurring MMP inhibitors include alpha-2 macroglobulin protein and tissue inhibitors of metalloproteinases (TIMPs), while tetracycline antibiotics, such as minocycline and doxycycline, are synthetic MMP inhibitors.[4]

Tetracyclines have been reported to competitively inhibit MMPs with a dose-dependent mechanism independent of their antimicrobial activity.[1 6–11] Previous research has demonstrated that doxycycline-mediated inhibition of MMPs reduces the rate of bone, cartilage and tendon degradation and thus has the ability to augment biological healing following musculoskeletal trauma or surgery.[2 12 13] Therefore, the purpose of this study was to describe the current orthopaedic uses for the non-antimicrobial application of doxycycline and to review its efficacy in musculoskeletal pathologies.

Historically, doxycycline has been used primarily as an antibiotic that acts through inhibition of bacterial protein synthesis. Doxycycline has a broad range of antimicrobial coverage and has been used for both gram-negative and gram-positive treatment and prevention of infections. For superficial skin infections, upper respiratory infection, uncomplicated community acquired pneumonia and other minor infections, doxycycline is generally dosed at 100 mg two times a day. However, for more complex infections and prophylactic use, 100 mg and higher can be prescribed for extended periods of time. Photosensitivity, abdominal pain and nausea are common side effects that have been reported with the use of doxycycline.

This review will consider the non-antimicrobial properties of doxycycline and will discuss both animal and human studies specific to the augmentation of healing of cartilage, tendon, ligament and bone pathologies. It will cover studies that examined these musculoskeletal pathologies in cellular testing environments, biomechanical labs and clinical outcomes. This study will not directly consider periodontal studies, embryological studies, case reports (level V evidence), editorial articles, surveys, or non-orthopaedic use of doxycycline.

CURRENT CONCEPTS

This study will provide a summary of 18 studies which were included in the review. One study used human mesenchymal stem cells and 17 studies studied the effects of doxycycline in animal models. Six studies examined doxycycline use in the setting of tendon injury or repair; 12 examined the effects of doxycycline on cartilage pathologies and 1 study evaluated the effects of doxycycline on osteoclast activity in bone; each of the studies included in tables 1 and 2 are considered controlled laboratory studies.

Effect of doxycycline usage on tendon healing

To date, there are six studies that investigated the effects of doxycycline on tendon pathologies used rat models.[1 2 14–17] Each of these studies investigated MMP levels and reported a significant decrease in MMP levels during at least one time-point with

Table 1 Doxycycline and tendon pathologies

Study (authors)	Target (study type)	Study overview and population	Treatment (doxycycline dose and route)	Statistically significant findings
Pasternak et al[14]	Tendon (Biomech)	60 rat Achilles tendons transected and left unrepaired. Recovery supplemented with doxy or placebo	130 mg/kg PO beginning POD −1	↓ Force at failure and energy uptake at 5, 8 and 14 days postop in all doxy groups =Cross-sectional area, stress and stiffness between groups
Arnoczky *et al*[2]	Tendon (Basic/Biomech)	225 stress deprived rat tail tendons treated with doxy vs control	50 µm/day for 7 days in media	↓ MMP-13 activity and ECM degradation in doxy-treated tendons ↑ Mechanical properties in doxy-treated tendons =MMP-13 mRNA compared with negative control at all time points
Pasternak *et al*[15]	Tendon (Biomech)	Rat Achilles tendon repair examined with systemic (n=80) vs local (n=33) doxy treatment	Phase 1: 100 mg/kg PO beginning POD −1 Phase 2: 30 ng/cm in sutures	=Biomechanical performance 3–7 days postop between systemic doxy and no treatment ↑ Force at suture pull-out and energy uptake 3 days postop in doxy coated sutures compared with uncoated sutures
Bedi *et al*[1]	Tendon (Basic/Biomech)	132 rats underwent acute detachment and repair of the supraspinatus tendon	130 mg/kg at various starting points	↓ MMP-13 activity in doxy treated tendons at POD 8 ↑ Metachromasia and collagen organisation at POD 5, 8 and 14 in doxy-treated tendons ↑ Load to failure at POD 14 in tendons treated preoperatively or POD 5 with doxy =Results/metrics between doxy and control groups at POD 28
Kessler *et al*[16]	Tendon (Basic/Biomech)	Doxy administration and MMP activity and repair quality of 100 severed rat Achilles tendons	10 mg/kg/day PO at various start points. LD=1 week preop ED=1 week preop +up to 3 weeks postrepair	↑ (Highest) MMP-8 levels at 4 weeks post transection in all groups ↓ MMP-8 activity with 4 weeks of doxy administration =MMP-8 activity with shorter durations (96 hours or 2 weeks) ↑ Collagen organisation, mechanical performance, histological score in the ED treatment compared with LD group. =Outcomes in LD limited duration treatment compared with control =Cross-sectional area between all groups
Nguyen *et al*[17]	Tendon (Basic/Biomech)	288 severed rat Achilles tendons either repaired or left transected. Half of each group received postop doxy (four groups total)	10 mg/kg PO beginning POD 1 to sacrifice	↑ Tissue organisation and biomechanical performance 6 weeks postinjury in repair w/ doxy ↓ Fibre dispersion, MMP-3 and TIMP1 9 weeks postinjury in repair w/ doxy =Cross-sectional area at all time points and biomechanical performance 9 weeks postinjury =Results in unrepaired tendons treated with doxy when compared with unrepaired with no doxy

↓ Indicates decreased, ↑ Indicates increased.
Biomech, biomechanical; Doxy, doxycycline; ECM, extracellular matrix; ED, extended duration; LD, limited duration; MMP, matrix metalloproteinase; PO, indicates oral administration; POD, postoperative day; TIMP, tissue inhibitors of metalloproteinases.

Table 2 Doxycycline and cartilage pathologies

Study (authors)	Target (study type)	Study overview	Treatment (dose and route)	Significant findings
Yu *et al*[18]	Cartilage (Basic/ Biomech)	OA induced in 12 dogs by transection of ACL with (n=5) or without (n=6) prophylactic doxy treatment	50 mg PO 2×/day for 8 weeks	↓ Collagenolytic activity, Mankin OA scores and knee effusion fluid volume in doxy treated dogs ↓ Severity of OA changes in medial compartment in treated dogs =Change in GAG synthesis between groups
Cole *et al*[19]	Cartilage (Basic)	Chick tibias removed from chickens at 12 days of embryonic development were cultured in media containing doxy vs no-doxy	Doxy in media at 5 ug/mL, 20 ug/mL or 40 ug/mL, changed every 2 days for 30 days	↓ Degradation of tibial cartilage, gelatinolytic enzymes and deposition of type X collagen in the matrix in tibias cultured with doxy ↑ Elongation of the region of hypertrophic cartilage with doxy
Steinmeyer *et al*[20]	Cartilage (Basic)	Proteoglycan content in IL-1 treated bovine articular cartilage (in vitro and in situ) compared in three different doxy concentrations	1, 10 and 100 µm of doxy in media, changed every 2 days for 10 days	↓ In proteoglycanolytic activity and IL-1 induced PG loss only significantly in the 100 uM doxy group
de Bri *et al*[21]	Cartilage (Basic/ Biomech)	In vivo and vitro model investigating doxy on spontaneous cartilage degeneration in 38 guinea pigs	20 mg/kg PO for 4 or 8 months	=OA changes were seen in doxy treated group compared to no treatment =OA changes were seen in doxy treated group compared to no treatment
Shlopov *et al*[22]	Cartilage (Basic)	Chondrocytes collected from patients (n=16) undergoing total knee arthroplasty secondary to OA treated with doxy compared to controls (n=5)	1, 10 or 50 ug/mL of doxy in media for 1 day	↑ MMP mRNA in chondrocytes isolated from OA knees ↓ In MMP-1, MMP-13, MMP-8, mRNA in all doxy treated media
Zhang *et al*[23]	Cartilage/ Bone (Basic)	(1) In vitro study of (i) osteoclastogenesis and (ii) OC fate with doxy treatment (2) In vivo study of doxy treatment on induced arthritis in mice	(1) (i) Doxy in media, replaced every 48 hours for 7 days; (ii) doxy added once for 3 days. (2) 2 mg/kg or 10 mg/kg by intraperitoneal injection daily	(1) (i) ↓ Both non-induced and induced OC formation with doxy treatment (ii) ↓ Mature OC bone resorption on cortical bovine slices with doxy (2) ↓ Area of osteolysis and osteoclastogenesis in doxy-treated mice compared to no doxy control groups
Blumberg *et al*[24]	Cartilage (Basic/ Biomech)	GAG release and mechanical properties were examined in bovine ulnas following low impact (LI) or high impact (HI)	0, 50 or 100 µm of doxy in media replaced every 24 hours for 1 or 2 weeks or for 2 weeks w/ doxy only added the first week	↑ Gross surface damage on in HI group regardless of doxy =Gross visualisation between LI group and non-impacted controls ↓ GAG release following HI in 100uM doxy group at 1-week and 2-week postimpact when compared to no treatment =GAG release between 2 weeks continuous treatment and 1 week on 1 week off
Nganvong-panit *et al*[25]	Cartilage (Biomech)	Dogs with pre-existing OA received doxy (n=12) or CS (n=13)	4 mg/kg/day doxy PO for 6 months, 525 mg/day CS PO for 6 months	= Radiograph scores between CS controls and doxy group ↑ Improvements in lameness, joint mobility, pain on palpation, weight-bearing and overall score at 2, 6, 4, 4 and 4 months, respectively, in doxy group compared to starting point ↓ Rate of OA improvements with doxy compared to CS
Bowyer *et al*[26]	Cartilage (Basic/ Biomech)	OA progression in 31 guinea pigs treated with and without doxy was observed	Surgically inserted pump: 0.6 mg/kg/day or 3.0 mg/kg/day for 66 days	↓ Medial tibial plateau cartilage loss and ↓JSN in both doxy treated groups =Levels (undetectable) of endogenous MMP activity in both groups ↓ MMP-9 proenzyme levels and ablated MMP-13 and MMP-8 levels in doxy treated group =MMP-1 proenzyme levels in doxy treated group compared to control
Fortier *et al*[27]	Cartilage (Basic)	SC and cartilage from horses either treated with IL-1 or MMP-13 and cultured with doxy	Doxy (4.3, 0.43, 0.043 µm) in media, changed at 48 hours	↓ GAG accumulation in media with all treatments of doxy ↓ MMP-3 and MMP-13 expression in SC but not cartilage with only the highest concentration of doxy
Lee *et al*[28]	Cartilage (Basic)	(1) Varying doxy doses on bone marrow derived mesenchymal stem cell (hMSC) pellets in media. (2) The effect of doxy on OA progression postsubchondral drilling in rats (n=12) compared to untreated controls (n=11)	(1) 0,1 or 2 ug/mL of doxy incubated for 3, 7, 14 or 21 days. (2) 2 mg/mL oral gavage for 12 weeks	↑ Cartilage area at 14 and 21 days in hMSC pellets treated with doxy =Proteoglycan, DNA, mRNA expression for chondrogenic genes between groups ↓ MMP-13 mRNA and protein at 21 days in hMSC pellets with 2 ug/mL doxy ↑ In vivo ICRS cartilage repair scores ↓ MMP-13 protein in doxy-treated rats
Zhang *et al*[30]	Cartilage (Basic/ Biomech)	Post-traumatic OA in 108 mice treated with varying concentrations of doxy	Doxy: 10, 50 or 100 mg/kg/day in water	↑ Symmetry in toe spread at 14 days with doxy ↓ Cartilage damage on histology with doxy ↓ Synovitis score with doxy ↓ MMP-13 activity, no significant difference between doxy concentrations *All doses had improved gait analysis *50 mg/kg/day had improved gait and histological appearance

↓ Indicates decreased, ↑ Indicates increased.
ACL, anterior cruciate ligament; bFGF, basic fibroblast growth factor; Biomech, biomechanical; CS, chondroitin sulfate; Doxy, doxycycline; ECM, extracellular matrix; ED, extended duration; EGF, epidermal growth factor; GAG, glycosaminoglycan; IL, interleukin; LD, limited duration; MMP, matrix metalloproteinase; OA, osteoarthritis; OC, osteoclast; PDGF, platelet-derived growth factor; PO, indicates oral administration; POD, postoperative day; SC, synoviocytes; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinases.

doxycycline treatment (table 1). While not consistently reported in each study, the reported time range for orally administered doxycycline to significantly alter MMP levels ranged from 7 days to 9 weeks postoperatively.[1 2 16 17] Other basic science variables that have been reported to be significantly improved by doxycycline treatment in the tendon pathology studies were the rate of ECM degradation,[2] collagen organisation,[1 2 17] metachromasia[1] and histological score.[16 17]

All six tendon healing studies tested the biomechanical properties influenced by doxycycline. Four studies demonstrated improved load to failure.[1 2 16 17] One study[15] demonstrated greater suture holding capacity when doxycycline coated sutures

were used for repair compared with uncoated sutures. Pasternak *et al*[15] reported no significant difference in the biomechanical performance of rat tendons systemically treated with doxycycline when compared with untreated controls (p=0.08). Only one study reported negative effects (decreased force and energy uptake at tendon failure during postoperative days 5–14) after doxycycline treatment.[14] There were no significant differences in the cross-sectional area of tendons treated with doxycycline when compared with untreated controls.[14 16 17]

The primary strengths of the tendon literature describing doxycycline use are in the consistent reported improvement in biomechanical and histological characteristics found with doxycycline administration, the variability in treatment delivery modalities (coated sutures and oral intake) and in the robust improvement seen with treatment. The primary weaknesses are that clinical trials have not been described and the variability in medication regimens (pretreatment and duration of treatment).

Effect of doxycycline usage on cartilage and bone

There are 12 preclinical studies that reported the effects of doxycycline on cartilage,[18–29] with one study[23] also reporting the effects of doxycycline on bone (table 2). There were 11 cartilage basic science studies, and 5 studies that assessed and demonstrated decreased MMP levels with doxycycline treatment.[20 21 24 29–31] Yu *et al*[18] reported no decrease in GAG synthesis, while three studies[20 27 31] reported significantly decreased GAG accumulation in cartilage or cartilage media treated with doxycycline. Additionally, there was one study that examined human mesenchymal stem cells and concluded that stem cells treated with both 1 µg/mL and 2 µg/mL of doxycycline in chondrogenic media produced samples with significantly increased cartilage area at 14 and 21 days.[28]

Five studies examined the mechanical properties of cartilage on doxycycline in animal models.[18 23 27 30 31] Four of these studies demonstrated improved biomechanical properties of cartilage, including decreased joint space narrowing, severity of osteoarthritis and cartilage functionality (table 1).[18 27 30 31] Only de Bri *et al*[21] reported no changes in cartilage or bone thickness, cartilage fibrillation, eburnation, horizontal separation or the volume densities of cartilage or bone in guinea pigs treated with doxycycline when compared with no treatment.

There was one study that investigated the effects of doxycycline on the progression of joint space narrowing and symptoms related to OA in canines.[25] This study found that 4 mg/kg/day of doxycycline treatment resulted in significant improvements in validated measures for lameness, joint mobility, pain on joint palpation, weight bearing ability and clinical outcome scores at 3 and 6 months compared with pretreatment levels.[25] Despite these improvements, there were no significant differences between the doxycycline group and the positive control (525 mg/day chondroitin sulfate) group on radiographic analysis. Furthermore, the positive symptomatic effects of doxycycline in canines all occurred at a slower rate when compared with the improvements seen in canines treated with chondroitin sulfate.

To date, there is only one clinical study known to the current authors that reported the symptomatic and radiographic effects of doxycycline. This study was a randomised control trial that included obese women with osteoarthritis diagnosed from standing radiographs. The experimental group was given 100 mg/kg doxycycline two times a day for 3 months. At the conclusion of the trial, the patients that received doxycycline demonstrated significantly less (33%) joint space narrowing compared with a placebo group; however, there were no differences in subjective outcome scores between groups. While mild side effects of doxycycline (gastrointestinal disturbance, sun sensitivity and so on) were observed, there were no serious adverse events attributable to doxycycline reported.[29]

Additionally, Zhang *et al*[23] studied the effect of doxycycline on bone. They reported that when doxycycline was added to osteoclastogenic media, the induced and non-induced activity of osteoclasts were significantly inhibited, resulting in decreased bone resorption compared with untreated controls.[23] Furthermore, they found that in vivo mice treated with doxycycline prior to induction of arthritis had significantly decreased osteoclastogenesis and areas of osteolysis.

The primary strengths of the cartilage studies that examined the effects of doxycycline were that multiple dosing recommendations were considered, multiple trials demonstrated improvements in histological and biomechanical markers and deceleration of joint space narrowing. Further, a clinical trial has been safely conducted with moderate effectiveness and few side effects. The weaknesses were that the results are variable, specifically the results pertaining to variations in dosing and that the results generally suggest that chronic doxycycline may be needed to be efficacious in these pathologies.

DISCUSSION

The primary concepts that were described in the current concept review were that doxycycline decreased MMP levels in both in vivo and in vitro models and that this reduction was linked to improved healing properties in both tendon and cartilage pathologies. Preclinical doxycycline studies reported improved tendon strength, organisation and histological scores in the acute setting and demonstrated decreased joint space narrowing in cartilage studies after chronic use. While these results are promising, additional clinical research is warranted to better understand the role that doxycycline mediated MMP inhibition can play in improving outcomes in musculoskeletal pathologies.

The ECM plays an integral role in cellular movement, cell-to-cell communication and the initiation of intracellular processing, among other functions. Major components of the ECM are collagens, which are primarily degraded by MMPs. The cyclic remodelling of collagen and turnover of the ECM is reliant on MMPs to maintain a healthy equilibrium.[32] There are currently 25 identified individual MMPs, and each MMP has a unique function.[33] Factors that increase the expression of MMPs are inflammatory cytokines (IL-1, IL-6, TNF-α) and growth factors (TGF-ß, EGF, PDGF and bFGF), whereas MMP expression can be inhibited by corticosteroids, retinoic acid, heparin and IL-4.[32] The catalytic activity of MMPs can also be silenced by endogenous TIMPs. When this equilibrium is dominated by excessive MMPs, fibrosis tends to occur, which leads to unhealthy ECM and tissue quality;[33] however, when MMP levels are below basal levels, studies have shown impaired ECM functions, including impaired cell-to-cell communication and intracellular cascade initiation.[34] Previous studies have also reported that exogenous MMP inhibitors such as doxycycline have no effect on TIMPs, suggesting that exogenous MMP inhibition must be carefully dosed so as to not overinhibit MMP functionality.[35]

Preclinical studies that examined doxycycline administration on tendinopathies primarily reported that doxycycline mediated MMP (MMP-3 to MMP-8 or MMP-13) inhibition after acute tendon injury and that increased postoperative tendon healing properties were observed days to weeks after injury.[1 2 15–17] Of note, Pasternak *et al*[15] reported no significant differences with systemic doxycycline treatment, but had they excluded those rats

that lost a significant amount of weight during the experimental phase (n=5), then the doxycycline treatment group would have demonstrated a significantly increased suture pull-out force. Pasternak *et al*[14] reported that doxycycline resulted in poorer biomechanical performance in transected rat tendons. However, these tendons were not surgically repaired, but rather allowed to heal by fibrous scar tissue. Thus, it can be inferred that the beneficial effects of doxycycline may be reserved to surgically repaired tendons and that doxycycline may not be effective at improving healing in tendons that have not been reapproximated.

Doxycycline mediated MMP inhibition displayed advantageous results in the majority of cartilage studies, although the results were not as robust as in the tendon studies. With doxycycline treatment, the majority of studies reported decreased progression of osteoarthritis and improved cartilage properties, including tensile strength and histological organisation.[18 19 21 23 25 26 28 30 31] However, two studies concluded that doxycycline had little benefit when compared with either positive controls or no treatment.[23 28] Nganvongpanit *et al*[25] concluded that doxycycline improved the symptomatic progression of OA in canines prior to starting treatment but demonstrated fewer improvements compared with chondroitin sulfate. de Bri *et al*[21] reported no significant benefit from doxycycline administration with respect to the progression of OA in guinea pigs compared with controls and significantly less benefit than chemically modified tetracycline. The benefit observed with chemically modified tetracycline suggests that certain classes of tetracycline derivatives may be more efficacious in the treatment of cartilage related pathologies than doxycycline. These inconsistencies in the reported effects of doxycycline on cartilage pathologies in both basic science and animal models detail the need for future clinical trials to study the efficacy of doxycycline for cartilage pathology.

Previous research[36] reported that MMP-1, MMP-2, MMP-9 and MMP-13 were significantly higher in the synovial fluid of patients with OA and rheumatoid arthritis (RA) when compared with controls. Of note, elevated MMP-3 levels within the synovium were found to be predictive for the development of RA at 2 years following sample collection.[37] These studies have postulated that the increased levels of MMPs significantly contribute to cartilage degeneration. These findings suggest that chronic MMP inhibition may provide beneficial effects in the treatment and prevention of OA, RA and other cartilage related conditions.

Doxycycline use for bony pathologies has yet to be thoroughly described in the orthopaedic literature, but it has been examined in the periodontal literature. Both clinical and preclinical studies have reported that doxycycline can potentiate the regenerative capacity of bony allografts and can therefore be used as a successful augmentation for the treatment of infrabony defects.[38–40] Given the success with doxycycline to augment bone grafting procedures in the periodontal literature and the relationship between MMP inhibition and improved healing properties observed in the preclinical studies on doxycycline, the current authors have begun using doxycycline as the standard of care for allograft bone grafting procedures and osteotomies for the past few years. During this time, these patients reported decreased swelling and less pain following these historically painful surgeries. Future prospective clinical trials to examine the potential use of doxycycline in these bony procedures should focus on objective outcomes and subjective patient reported pain.

Among studies included in the current review, doxycycline was administered at varying doses, durations and routes. Generally, there were reported benefits of chronic (months to years) administration of doxycycline on cartilage pathologies. In the single known clinical trial, chronic daily doses (100–200 mg) of doxycycline were reported to be effective in reducing the progression of cartilage degeneration in early osteoarthritis. However, the recent preclinical study from Zhang *et al*[30] on post-traumatic osteoarthritis demonstrated that 50 mg/kg, a subantimicrobial dose, is effective at reducing the progression of osteoarthritis is an animal model. These results are encouraging because these lesser doses may help avoid the adverse side effects associated with chronic antibiotic administration (box 1). Conversely, relatively shorter (days to weeks) durations of doxycycline administration in preclinical studies benefitted tendon healing postsurgical repair. Of note, despite the large variations in doxycycline dosing, only mild side effects in humans (commonly gastrointestinal related) and animals (ie, weight loss due to altered water taste) were reported.[15 25]

Box 1 Most Common Doxycycline Side Effects

- Weight loss
- Vomiting
- Rash
- Discoloration of Teeth
- Anemia
- Nausea
- Diarrhea
- Skin Sensitivity to Sun
- Hives

An additional consideration associated with doxycycline is its anti-inflammatory properties. Doxycycline has been shown to inhibit production of IL-1ß in addition to other cytokines, which leads to T-cell activation.[41 42] While decreased inflammation can lead to the symptomatic improvement (pain, gait, lameness and so on) observed in the included studies, each of the studies discussed MMP inhibition as the primary target of doxycycline. Future studies involving the use of doxycycline in tendon and cartilage pathologies should be designed to examine the anti-inflammatory properties in addition to the MMP inhibitory properties discussed in the current review.

The authors acknowledge some limitations in the current review. Most studies reviewed used animal models, which may limit the generalisability of results to human subjects. Artificial tendon injuries were created surgically, which may not be generalisable to the natural pathology of tendon tears. Furthermore, only acute tendon injuries were examined in the included studies, rather than a combination of acute pathologies with chronic tendinopathies. Some studies included implemented in vitro models which may not translate to in vivo models. The heterogeneity of doxycycline dosing, route, duration, experimental design used and measured outcome variables limited the comparison of studies to one another and potentially limits their translation to clinical trials.

CONCLUSION

Doxycycline use was associated with improved healing properties in various tendon and cartilage pathologies. In preclinical trials, improved healing properties were observed acutely in tendon injuries and chronically in cartilage injuries. Furthermore, doxycycline was well tolerated with minimal side effects reported in clinical and preclinical studies. While it can be reasonably inferred that the positive effects of doxycycline are related to

its ability to inhibit MMP activity, further clinical research is warranted to investigate the use of doxycycline in orthopaedic and musculoskeletal pathologies.

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