Complications Associated With the Use of Corticosteroids in the Treatment of Athletic Injuries

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Background: The potent anti-inflammatory pharmacologic effects of the corticosteroids (cortisone and synthetic derivatives) has led to their extensive usage in the management of rheumatologic diseases and athletic musculoskeletal injuries. The efficacy and risks of locally injected or systemically administered corticosteroids in the treatment of athletic injuries are unclear.

Objective: To review critically the medical literature and determine complications and risks associated with corticosteroid treatment of athletic injuries.

Data Sources: A search of 3 databases—MEDLINE, CINAHL, and Cochrane Clinical Trial Register—was performed using the OVID interface for all years between 1966 and 2003. The search first combined all references under the medical subject headings *adrenal cortex hormones*, *glucocorticoids*, and *glucocorticoids, synthetic*. A second search combined all references under the medical subject headings *athletic injuries*, *sprains and strains*, *tendon injuries*, *shoulder injuries*, *rotator cuff disease*, *tennis elbow*, and *lateral epicondylitis*. The references identified by these 2 searches were intersected and limited to *human only* to produce 130 articles. Relevant review articles were scanned, references reviewed, and additional articles retrieved for consideration of inclusion.

Study Selection: For inclusion in this critical review, articles must meet the following criteria: (1) subjects were human, (2) subjects had athletic-related injuries, and (3) subjects received corticosteroid treatment. Ultimately, 43 studies met inclusion criteria.

Data Extraction and Synthesis: Selected articles were then categorized as to whether the primary focus was usage/efficacy of corticosteroid injection therapy, occurrence of complications of corticosteroid injection therapy, or usage or complications of systemic corticosteroid therapy.

Main Results: Twenty-five selected studies primarily examined the usage/efficacy of corticosteroid injections in the treatment of various athletic injuries. Of the 983 total subjects who received corticosteroid injections among these studies, only minor complications of treatment were reported. Eighteen selected studies primarily described complications of corticosteroid injections in the treatment of athletic injuries. Of these, tendon and fascial ruptures were the predominant complications reported. The search identified no articles that addressed the usage of or complications of systemic corticosteroids in the treatment of athletic injuries, although tibial stress fracture and multifocal osteonecrosis occurred in individuals being treated for nonathletic injury conditions.

Conclusions: This critical review reveals that the existing medical literature does not provide precise estimates for complication rates following the therapeutic use of injected or systemic corticosteroids in the treatment of athletic injuries. Tendon and fascial ruptures are often reported complications of injected corticosteroids, whereas tibial stress fractures and multifocal osteonecrosis were described with systemic corticosteroids.

Key Words: adrenal cortex hormones, glucocorticosteroids, glucocorticoids, synthetic, athletic injuries, sprains and strains, tendon injuries

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Cortisone was first used to treat rheumatoid arthritis in 1949.[1] The subsequent synthesis of a hydrocortisone crystal acetate suspension derivative from the cortisone molecule led to improved pharmacologic availability and extensive clinical usage of various corticosteroid agents in the management of rheumatologic diseases.[2] Hollander noted that "no other form of treatment has given such consistent local symptomatic relief in so many for so long with so few harmful effects."[3,4] In contrast, other authors found intra-articular corticosteroid injections to be ineffective in relieving osteoarthritis symptoms.[5–10]

The evolving recognition of serious adverse effects associated with cortisone therapy led to a shift away from systemic administration and toward intra-articular, intrabursal, and peritendinous injections. During the 1960s, intra-articular corticosteroid injections became widely used by sports medicine physicians to treat professional athletes.[11] Physicians continue to use corticosteroid injections to treat a wide range of musculoskeletal disorders.[12] Corticosteroid injections have been reported to be effective in treating supraspinatus tendinitis,[13] lateral epicondylitis,[14,15] iliotibial band syndrome,[16,17] acromioclavicular ligament sprain,[18] hand flexor digitorum stenosing tenosynovitis,[19,20] DeQuervain tenosynovitis,[21,22] foot tendinopathies,[23] osteitis pubis,[24,25] bucket-handle tears of the medial plica,[26] and Achilles tendinitis with tendon-paratenon adhesions.[27,28]

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Corticosteroids are associated with numerous adverse effects, including those resulting from systemic administration (eg, hypertension, glucose intolerance, Cushing habitus, and so forth) and those associated with local injections (eg, articular cartilage damage, tendon rupture, skin depigmentation, and so forth). This article reviews the medical literature to critically assess the risks of using corticosteroids in the treatment of athletic injuries.

METHODS

A search of 3 databases—MEDLINE, CINAHL, and Cochrane Clinical Trial Register—was performed in December 2003, using the OVID interface for all years between 1966 and 2003. Although review articles were excluded, the reference lists of particularly relevant review articles were scanned to identify additional articles that contain data central to this study. Articles were selected for inclusion in the review based upon meeting the following criteria: (1) subjects were human, (2) subjects had athletic-related injuries, and (3) subjects received corticosteroid treatment. The definition of *athletic-related injuries* was musculoskeletal injuries or conditions that occurred commonly as a result of athletic activity or other repetitive physical activity.

To account for biases of published studies, articles were separated further into groups based upon whether the primary focus was (1) the "usage/efficacy of corticosteroid injections for athletic injuries," ie, those not primarily reporting complications of corticosteroid injections; and (2) the "occurrence of complications due to corticosteroid injections for athletic injuries," ie, those primarily reporting complications of corticosteroid injections. The review also involved a search for articles that examined the "usage or complications of systemic corticosteroids for athletic injuries."

RESULTS

Literature Search Results

The search strategy, summarized in Table 1, produced 130 references. Ultimately, 43 articles were determined to meet inclusion criteria. Twenty-five clinical studies included in the review primarily examined the usage of corticosteroid injections in the treatment of athletic injuries with secondary mention of complication occurrence (Table 2, group A). Eighteen articles were found that primarily describe complications associated with corticosteroid injections in the treatment of athletic injuries (Table 2, group B). No studies were identified that discussed the usage or complications of systemic corticosteroids in the treatment of athletic injuries. Overall, a total of 1078 human subjects received corticosteroid injections for the treatment of athletic injuries in Table 2. Of these, 244 (22.6%) experienced complications associated with such therapy.

TABLE 1. Ovid MEDLINE, CINAHL, and CCTR Search Strategy from 1966–2003

Step	Search Strategy	Results
1	Adrenal cortex hormones	31,504
2	Glucocorticosteroids OR glucocorticoids, synthetic	37,224
3	1 OR 2	67,806
4	Athletic injuries OR "sprains and strains" OR tendon injuries	24,610
5	Shoulder injuries OR rotator cuff disease	1,021
6	Tennis elbow OR lateral epicondylitis	1,155
7	4 OR 5 OR 6	26,305
8	3 AND 7	136
9	Limit 8 to human	130

Clinical Series That Primarily Describe the Usage/Efficacy of Local Corticosteroid Injection Therapy for Athletic Injuries in Which Complications Are Reported Secondarily

To limit biases that may be introduced by reviewing only articles that report complications of corticosteroid injection therapy for athletic injuries, this review first identified studies on the usage of corticosteroid injection therapy and not the occurrence of complications as the primary reason for publication. Twenty-five such clinical studies are included in Table 2 (group A). Of these, 22 are randomized clinical trials that evaluate the efficacy of corticosteroid injections in the treatment of lateral (or medial) epicondylitis, shoulder injuries, or Achilles paratendonitis. The remaining articles included are retrospective, observational reports of corticosteroid injection therapy efficacy in the management of osteitis pubis and hamstring strains.

Of the 983 patients in the 25 included studies who received corticosteroid injections to treat various athletic injuries, 149 subjects reported side effects or complications of therapy (15.2%). Postinjection pain was the most common side effect, as noted by 95 subjects (9.7%). Other complications were reported by 54 subjects, including skin atrophy in 24 (2.4%), skin depigmentation in 8 (0.8%), localized erythema and warmth in 7 (0.7%), and facial flushing in 6 (0.6%). If postinjection site pain is excluded from consideration as a complication, the resulting complication rate of corticosteroid injection treatment of human athletic injuries from these studies is 5.5%.

Case Series/Reports That Primarily Describe Complications Associated With Corticosteroid Injections Therapy for Athletic Injuries

Eighteen of the retrieved articles primarily described complications that occurred in association with corticosteroid injection therapy for various athletic-related injuries (Table 2, group B). Among medical conditions being treated in these cases were various tendinitis types (Achilles, patellar, quadriceps, infrapatellar), plantar fasciitis, lateral epicondylitis, shin splints, and olecranon bursitis. Of the total 95 subjects in these case series or reports, all 95 (100%) developed complications. Plantar fascia rupture was the most common complication, as reported in 51 subjects (53.7%). Less frequent complications included patellar/quadriceps tendon rupture in 9 (9.5%), Achilles tendon rupture in 8 (8.4%), biceps tendon rupture in 8 (8.4%), and subcutaneous atrophy in 7 (7.4%). Lateral epicondyle origin, supraspinatus, tibialis anterior, biceps

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TABLE 2. Studies on the Usage, Efficacy, and Complications of Corticosteroid Injection Treatment of Human Athletic Injuries

Investigation (Reference)	Study Type	Medical Condition Treated	No. Subjects Treated	No. Complications (All)	No. Complications (Not "Pain")
Group A. Study purpose: to report on the usage/efficacy of corticosteroid injections primarily; complications are reported secondarily					
Adebajo et al, 1990 (53)	RCT	Rotator cuff tendinitis	20	15	
Bar et al, 1997 (61)	RCT	Lateral epicondylitis	246	6	6
Batt et al, 1995 (24)	Observational	Osteitis pubis	2		
Berry et al, 1980 (55)	RCT	Painful shoulder from rotator cuff lesion	24		
Blair et al, 1996 (62)	RCT	Subacromial impingement syndrome	40		
DaCruz et al, 1988 (27)	RCT	Achilles paratendonitis	14		
Day et al, 1978 (14)	RCT	Lateral epicondylitis	36		
Erturk et al, 1997 (63)	RCT	Lateral epicondylitis	19		
Haker et al, 1993 (64)	RCT	Lateral epicondylitis	19	2	
Halle, 1986 (65)	RCT	Lateral epicondylitis	12		
Hay et al, 1999 (66)	RCT	Lateral epicondylitis	53	5	
Holt et al, 1995 (25)	Observational	Osteitis pubis	11		
Kirkley et al, 1999 (67)	RCT	Rotator cuff tendinosis	21		
Levine et al, 2000 (68)	Observational	Hamstring strains	58		
Newcomer et al, 2001 (69)	RCT	Lateral epicondylitis	20		
Oksenberg et al, 1998 (70)	RCT	Lateral epicondylitis	14		
Petri et al, 1987 (71)	RCT	Painful shoulder	50	1	1
Price et al, 1991 (72)	RCT	Lateral epicondylitis	89	71	24
Sartok et al, 1986 (73)	RCT	Lateral epicondylitis	11	3	
Shibata et al, 2001 (74)	RCT	Rotator cuff tear	39		
Smidt et al, 2002 (75)	RCT	Lateral epicondylitis	62	38	22
Stahl and Kaufman, 1997 (16)	RCT	Medical epicondylitis	30	1	1
Vecchio et al, 1993 (76)	RCT	Rotator cuff tendinitis	28	7	
Verhaar et al, 1996 (77)	RCT	Lateral epicondylitis	53		
Withrington et al, 1985 (78)	RCT	Supraspinatus tendinitis	12		
Group 1 subtotal+C43:			983	149 (15.2%)	54 (5.5%)
Group B. Study purpose: to report complications of corticosteroid injections primarily; usage/efficacy is reported secondarily					
Acevedo and Beskin, 1998 (79)	Case series	Plantar fasciitis	41	41	
Ahstrom, 1988 (80)	Case series	Plantar fasciitis	5	5	
Baack et al, 1991 (81)	Case report	DeQuervain's tenosynovitis	1	1	
Chechick et al, 1982 (82)	Case report	Achilles tendinitis	1	1	
Ford et al, 1979 (83)	Case series	Various forms of tendinitis and bursitis	15	15	
Gottlieb et al, 1980 (84)	Case report	Carpal tunnel syndrome	1	1	
Ismail et al, 1969 (85)	Case report	Patellar tendinitis	1	1	
Jones, 1985 (86)	Case report	Achilles tendinitis	1	1	
Kelly et al, 1984 (87)	Case series	Patellar or quadriceps tendinitis	8	8	
Kleinman et al, 1983 (88)	Case series	Achilles tendinitis	3	3	
Leach et al, 1978 (89)	Case series	Plantar fasciitis	5	5	
Matev, 1991 (90)	Case report	Hamstring strain	1	1	
McFarland et al, 1990 (91)	Case report	Infraspinatus tendinitis	1	1	
Rostron et al, 1979 (92)	Case series	Osgood's-Schlatter's Disease	7	7	
Smith et al, 1999 (93)	Case report	Lateral epicondylitis	1	1	
Stannard et al, 1995 (94)	Case report	Olecranon bursitis	1	1	
Taras et al, 1995 (95)	Case report	Trigger thumb	1	1	
Velan, 1997 (96)	Case report	Shin splints	1	1	
Group 2 subtotal:			95	95 (100%)	NR
Overall total:			1078	244 (22.6%)	

Investigation (Reference)	Corticosteroid Injection Agents	Complications Reported	Comments
Group A. Study purpose: to report on the usage/efficacy of corticosteroid injections primarily; complications are reported secondarily			
Adebajo et al, 1990 (53)	Triamcinolone hexacetonide	Postinjection pain (15)	
Bar et al, 1997 (61)	Dexamethasone	Localized warmth (1), facial flush (3), localized erythema (1), local ecchymosis (1)	

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TABLE 2. (*Continued*) Studies on the Usage, Efficacy, and Complications of Corticosteroid Injection Treatment of Human Athletic Injuries

Investigation (Reference)	Corticosteroid Injection Agents	Complications Reported	Comments
Batt et al, 1995 (24)	Betamethasone	None	
Berry et al, 1980 (55)	Methylprednisolone	None	
Blair et al, 1996 (62)	Triamcinolone acetonide	None	
DaCruz et al, 1988 (27)	Methylprednisolone acetate	None	
Day et al, 1978 (14)	Methylprednisolone	None	
Erturk et al, 1997 (63)	Triamcinolone acetonide	None	
Haker et al, 1993 (64)	Triamcinolone acetonide	Postinjection pain (2)	
Halle, 1986 (65)	Hydrocortisone	None	
Hay et al, 1999 (66)	Methlyprednisolone	Post+H31 injection pain (5)	
Holt et al, 1995 (25)	Dexamethasone	None	
Kirkley et al, 1999 (67)	Betamethasone	None	
Levine et al, 2000 (68)	Dexamethasone sodium acetate, triamcinolone hexacetonide or triamcinolone acetonide	None	
Newcomer et al, 2001 (69)	Betamethasone	None	
Oksenberg et al, 1998 (70)	Betamethasone	None	
Petri et al, 1987 (71)	Triamcinolone	Local skin depigmentation (1)	
Price et al, 1991 (72)	Triamcinolone (60) or hydrocortisone (29)	Postinjection pain (triamcinolone = 28; hydrocortisone = 17); skin atrophy (triamcinolone = 18; hydrocortisone = 6)	
Sartok et al, 1986 (73)	Betamethasone	Postinjection pain (a few cases)	
Shibata et al, 2001 (74)	Dexamethasone	None	
Smidt et al, 2002 (75)	Triamcinolone acetonide	Postinjection pain (16), facial flush (2), skin erythema (5), change in skin color (7), other minor reactions (8)	
Stahl and Kaufman, 1997 (16)	Methylprednisolone	Facial flushing (1)	
Vecchio et al, 1993 (76)	Methylprednisolone	Mild transient post+H40 injection pain (7)	
Verhaar et al, 1996 (77)	Triamcinolone acetate	None	
Withrington et al, 1985 (78)	Methylprednisolone	None	
Group 1 subtotal+C43:			
Group B. Study purpose: to report complications of corticosteroid injections primarily; usage/efficacy is reported secondarily			
Acevedo and Beskin, 1998 (79)	Various	Plantar fascia ruptures	
Ahstrom, 1988 (80)	Various	Plantar fascia ruptures	In each case, symptoms resolved 3–4 wk after rupture
Baack et al, 1991 (81)	Triamcinolone	Mycobacterium chelonei infection	3 y after dorsal compartment injection
Chechick et al, 1982 (82)	Triamcinolone	Recurrent achilles tendon rupture	
Ford et al, 1979 (83)	Triamcinolone hexacetonide	Tendon ruptures: biceps (8), Achilles (3), supraspinati (2), lateral epicondylar attachment (1), tibialis anterior (1)+H17	
Gottlieb et al, 1980 (84)	Triamcinolone	Multiple digital flexor tendons	29 injections within 6 mo
Ismail et al, 1969 (85)	Triamcinolone	Patellar tendon rupture	High jumper, 4 injections in 1 y, no rest from training
Jones, 1985 (86)	Triamcinolone	Achilles tendon rupture	
Kelly et al, 1984 (87)	Various	Patellar or quadriceps tendon ruptures	Most subjects received >3 injections; 1 received 12
Kleinman et al, 1983 (88)	Various	Achilles tendon rupture	One subject also received systemic corticosteroids
Leach et al, 1978 (89)	Various	Plantar fascia partial rupture	
Matev, 1991 (90)	Various	Contracture of long head of biceps femoris	Soccer player, recovered after surgical release
McFarland et al, 1990 (91)	Triamcinolone	Axillary nerve injury	
Rostron et al, 1979 (92)	Various agents	Subcutaneous atrophy	
Smith et al, 1999 (93)	Triamcinolone	Rupture of the common extensor tendon origin	

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TABLE 2. (*Continued*) Studies on the Usage, Efficacy, and Complications of Corticosteroid Injection Treatment of Human Athletic Injuries

Investigation (Reference)	Corticosteroid Injection Agents	Complications Reported	Comments
Stannard et al, 1995 (94)	Various	Triceps tendon rupture	Multiple olecranon bursal injections, history of anabolic steroid abuse
Taras et al, 1995 (95)	Triamcinolone	Flexor pollicis longus tendon rupture	
Velan, 1997 (96)	Triamcinolone	Tear of tibialis anterior tendon	

femoris, triceps, and hand and finger flexor tendon ruptures were also reported, as was axillary nerve injury and *Mycobacterium* infection.

DISCUSSION

Cortisone and its synthetic derivatives exert potent anti-inflammatory pharmacologic effects by inhibiting granulation tissue formation, collagen precursor ground substance sulfation, fibroblast and blood vessel formation, and collagen tissue repair.[29–31] Inflammation is the primary pathology in various rheumatologic diseases, whereas the inflammation of athletic injuries is a secondary response to musculoskeletal trauma. It thus seems possible that the anti-inflammatory pharmacologic effects of corticosteroids may differ in therapeutic effects when used to treat the 2 types of conditions. Further, citing the therapeutic role of inflammation as an essential step in the healing of acute musculoskeletal injuries, numerous authors suggest that corticosteroids should be completely avoided for the treatment of athletic injuries.[9,13–16,18,22,24–26,32,33]

The formulation of evidence-based treatment guidelines requires scientific analyses of the benefits and risks of a particular treatment modality or pharmacologic agent in the treatment of a specific medical condition. This critical review examines the medical literature to assess risks associated with the use of corticosteroids in the treatment of athletic injuries. The search failed to identify any published articles that evaluate efficacy or complications of systemic corticosteroids in the treatment of athletic injuries. Thus, the paper is limited to a discussion of complications of corticosteroid injection treatment of athletic injuries. In determining clinical treatment guidelines, minor complications of corticosteroid injections (eg, postinjection pain, local flare reaction, skin depigmentation, and skin dimpling) are more acceptable than serious complications (eg, osteonecrosis and tendon rupture). A further consideration is that athletes routinely place extraordinary stresses on musculoskeletal structures that may further predispose to corticosteroid associated tendon rupture, ligament weakening, and articular cartilage damage.

The literature search did not identify studies that provide unequivocal scientific evidence that corticosteroid injections do or do not cause damage to human musculoskeletal structures. Although not the objective of this critical review, Table 3 summarizes 17 animal studies that examine the effects of corticosteroid injections on the structure and function of tendons, ligaments, or articular cartilage. Of these, 10 investigations provide evidence that corticosteroid injections cause musculoskeletal structural or functional damage, and 7 do not.

Ten such animal studies examined the effects of corticosteroid injections on tendons. Peritendinous rat Achilles tendon injections did not reduce tendon strength to failure.[34] Intratendinous rabbit patellar,[5] Achilles,[6] and gastrocnemius[9] tendon injections were associated with decreased tensile strength, weight, load to failure, and energy. Other investigators found no such negative effects.[35–37] Subacromial bursal injections were associated with rat rotator cuff tendon damage,[38] whereas local injections did not hinder the healing of recently sutured tendons.[39,40]

Two animal studies examined the effects of corticosteroid injections on ligaments. Intra-articular rhesus monkey knee injections of high-dose (but not low-dose) corticosteroids produced reduced load tolerance and energy to failure of the anterior cruciate ligaments for at least 15 weeks after injection.[8] High-dose corticosteroid intra-articular knee injections in rats were found to cause medial collateral ligament stiffness and a similar reduction in peak load for at least 3 weeks.[10]

Five animal studies considered the effects of corticosteroid injections on articular cartilage. Intra-articular rabbit knee injections caused decreases in articular cartilage chondrocyte glycine utilization and protein synthesis,[41,42] delayed articular cartilage repair, and the development of articular cartilage fissures and cystic changes.[15] On the other hand, injections into osteoarthritic dog knees were found to slow the progression of articular cartilage degeneration.[43] Rats trained in a running program who also received intra-articular hydrocortisone knee injections showed histologic evidence of articular cartilage damage compared with rats who received injections alone or were trained in running alone.[44] In summary, the variety of study protocols, sites of injections, corticosteroid agents and dosages, dependent variables measured, frequent absence of controls, and animal species models used prevent the direct application of these findings to human subjects.

The literature suggests that the choice of corticosteroid agent to treat human tendon injuries may affect posttreatment tendon strength. Tendons treated with triamcinolone acetonide seem to develop more frequent mechanical structural defects and a higher tendency to rupture than those treated with methylprednisolone, betamethasone, or hydrocortisone. Further, the relative doses of corticosteroids administered may influence on posttreatment mechanical tendon properties. Injection technique may also influence the occurrence of complications as intratendinous injection may damage tendons via mechanical disruption.

The search did not identify studies that examined adverse effects of intra-articular corticosteroid injections in the

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TABLE 3. Effects of Corticosteroid Injections on Musculoskeletal Structures in Animals

Investigation (Reference)	Animal Model	Anatomic Structure	Intervention	Design
Tendons				
Gonzales, 1953 (39)	Dogs	Recently sutured flexor tendons	Local injection of hydrocortisone around the site of repair	Placebo-controlled
Grant, 1953 (40)	Rabbits	Recently sutured patellar tendons	IM CS injections	Placebo-controlled
Kapetanos, 1982 (5)	Rabbits	Patellar tendons	Repeated small dose intra-tendinous triamcinalone vs. saline control injections	Placebo-controlled
Kennedy et al, 1976 (6)	Rabbits	Achilles tendons	Local injection of betamethasone vs. no injection	Placebo-controlled
Mackie et al, 1974 (35)	Rabbits	Achilles tendons	Repeated CS injections into tendons vs. no injections	Placebo-controlled
Matthews et al, 1975 (36)	Rabbits	Patellar tendons	Intratendinous injections of hydrocortisone vs. no injections	Placebo-controlled
McWhorter et al, 1991 (34)	Rats	Achilles tendons	Peritendinous injections of hydrocortisone vs. no injection	Placebo-controlled
Phelps et al, 1974 (37)	Rabbits	Patellar tendons	Intratendinous injections of hydrocortisone vs. no injections	Placebo-controlled
Tillander et al, 1999 (38)	Rats	Supraspinatus and infraspinatus tendons	3 or 5 injections with human dose triamcinolone or 3 or 5 injections with saline into subacromial space	Placebo-controlled
Unverferth et al, 1973 (9)	Rabbits	Gastrocnemius tendons	Intratendinous injections of hydrocortisone vs. no injections	Placebo-controlled
Ligaments				
Noyes et al, 1977 (8)	Rhesus monkeys	Knee ACLs	High-dose (10X human physiologic equivalent) methylprednisolone acetate intra-articular injection vs. low dose (human physiologic dose)	Placebo-controlled
Wiggins et al, 1994 (10)	NZ White rabbits	Knee MCLs	Low-dose (physiologic equivalent) and high-dose (human therapeutic equivalent dose) intra-articular betamethasone injections, and saline injections	Placebo-controlled (saline injections)
Articular cartilage				
Behrens et al, 1975 (41)	Rabbits	Knee articular cartilage	Repeated intra-articular hydrocortisone acetate injections	Descriptive
Gogia et al, 1993 (44)	Rats	Knee articular cartilage	3 groups (n = 12 each): intra-articular hydrocortisone injections vs. intra-articular HC injections plus running vs. running alone	Placebo-controlled
Mankin, 1966 (42)	Rabbits	Knee articular cartilage	Intra-articular CS injection	Placebo-controlled
Pelletier et al, 1991 (43)	Dogs	Knee articular cartilage	Intra-articular triamcinalone injections in ACL-sectioned OA model knees	Placebo-controlled
Roach et al, 1975 (97)	Rabbits	Knee articular cartilage	Intramuscular prednisolone vs. oral aspirin given to subjects with experimentally D14induced articular cartilage damage	Cross+E9over

Investigation (Reference)	Dependent Variables	Results	Deleterious Effects of Corticosteroids?
Tendons			
Gonzales, 1953 (39)	Effect on healing of sutured tendon	Tendon healing was not inhibited by local infiltration of CS	No
Grant, 1953 (40)	Effect on healing of sutured tendon	IM injection of CS had no deleterious effect upon healing of a recently sutured tendon	No
Kapetanos, 1982 (5)	Tendon weight, load to failure, and energy to failure; also, functional strain and healing+F19	Resulted in reductions in tendon weight (13%), load to failure (30%), and energy to failure (67%); no significant differences in functional strain and healing of tendon	Yes
Kennedy et al, 1976 (6)	Tendon strength to failure	Tendon strength to failure was reduced by 35% at 48 h after betamethasone injection; strength returned to normal after 2 wk	Yes
Mackie et al, 1974 (35)	Mechanical properties of tendons	No significant change in mechanical properties	No
Matthews et al, 1975 (36)	Maximum tendon load, stiffness, and biochemical properties	No adverse effects on tendon stiffness, maximum load, or biochemical properties	No
McWhorter et al, 1991 (34)	Tendon strength to failure, histologic inflammatory response	No adverse effect on tendon strength	No
Phelps et al, 1974 (37)	Maximum load, stiffness, and biochemical properties	No adverse effects on tendon stiffness, maximum load, or biochemical properties	No
Tillander et al, 1999 (38)	Histologic staining analysis of tendons	Pathologic changes of focal inflammation, necrosis, and fragmentation of collagen bundles in the tendon of 4 of 7 rats that received 5 CS injections; the others showed no detrimental effects on the RCs	Yes
Unverferth et al, 1973 (9)	Tendon mechanical properties	Reduced tendon stiffness and lower tensile strength	Yes

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TABLE 3. (*Continued*) Effects of Corticosteroid Injections on Musculoskeletal Structures in Animals

Investigation (Reference)	Dependent Variables	Results	Deleterious Effects of Corticosteroids?
Ligaments			
Noyes et al, 1977 (8)	Ligament load tolerance	High-dose CS resulted in reduction in maximum failure load (20%), energy absorption prior to failure (11%), and tendon stiffness (11%) at 15 wk; clinically insiginificant ligament strength reductions occurred with low-dose (human therapeutic equivalent) injections	Yes
Wiggins et al, 1994 (10)	Ligament mechanical properties	Reduced peak load and stiffness of MCLs at 10 days and at 3 wk in the high-dose CS group compared to low-dose CS and saline groups.	Yes
Articular cartilage			
Behrens et al, 1975 (41)	Adverse effects on articular cartilage and metabolism.	Associated with articular cartilage fissures, cystic changes, reduced proteoglycan and protein synthesis	Yes
Gogia et al, 1993 (44)	Femoral surface articular cartilage degeneration	"HC + run" rats displayed fibrotic invasion and/or subchondral bone replacement of degenerated articular cartilage and areas of cell death compared to other 2 groups	Yes
Mankin, 1966 (42)	Articular cartilage metabolism	Decrease in chondrocyte glycine utilization and protein synthesis in a dose-dependent manner	Yes
Pelletier et al, 1991 (43)	Development of OA changes (osteophyte formation) and articular cartilage damage	Delayed appearance of OA changes and articular cartilage damage in OA model in dogs treated with CS injections	No
Roach et al, 1975 (97)	Articular cartilage status after 3 wk	Accelerated articular cartilage degeneration in the group receiving CS	Yes

management of athletic injuries. However, Table 4 summarizes 3 studies that examined these effects in subjects with arthritis. Salient findings are that the number of intra-articular corticosteroid injections received appears to correlate both with more severe disease at the time of arthritis surgery[45] and with radiographic acceleration in joint deterioration.[46]

Complications associated with corticosteroid injection treatment of athletic injuries and of nonathletic injury medical conditions are comparatively listed in Tables 2 and 5, respectively. Tendon rupture is the predominant complication reported in the athletic injury corticosteroid injection treatment groups, whereas systemic adverse effects occur more commonly in the nonathletic injury series. Perhaps it is both the systemic nature of the underlying disease process (eg, rheumatoid arthritis, JRA, HLA-B27 arthritis) and the higher number of injections received in the nonathletic injury groups that may account for these apparent differences. Osteonecrosis of the femoral and humeral heads, a devastating complication of corticosteroid injection therapy, was not found to occur following the corticosteroid injection treatment of any athletic injury conditions.

Studies that primarily evaluated the usage or efficacy of corticosteroid injections, with secondary reporting of complications (Table 2, group A), identified the occurrence of relatively few complications. Because these studies did not report complications as the primary topic, and often had short

TABLE 4. Effects of Intra-Articular Corticosteroid Injections on Joints in Humans

Investigation (Reference)	Medical Condition Treated	Intervention	Design	Dependent Variables	Results	Deleterious Effects of Corticosteroids?
Balch, 1977 (98)	Knees affected by rheumatoid arthritis or osteoarthritis over 4–15 y (n = 65)	Multiple intra-articular CS injections	Retrospective	Gross joint deterioration on plain x-rays	Gross joint deterioration did not correlate with the number of injections received, but instead with the severity of disease	?
Chandler, 1958 (46)	Knee OA (n = 15)	Multiple intra-articular CS injections	Retrospective	Radiographic evidence of arthritis	Rapid deterioration in the radiographic appearance of arthritic knees treated with intra-articular CS injections	Yes
Salter, 1967 (45)	Subjects with various types of arthritis	Multiple intra-articular CS injections	Retrospective	Articular cartilage deterioration observed at arthritis management surgery	Strong correlation between degree of articular cartilage degeneration and the number of CS injections received	Yes

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TABLE 5. Complications of Corticosteroid Injections in the Treatment of Nonathletic Injuries in Humans

Investigation (Reference)	Medical Condition Treated	Number of Subjects	Corticosteroid Injection Agents	Complications	Comments
Job-Deslandre et al, 1990 (99)	Juvenile RA and HLA-B27 arthritis	35 with JRA, 13 with HLA-B27	Triamcinalone hexacetonide	Subcutaneous atrophy with depigmentation developed in 8.3% and intra-articular calcifications in 4.9%	Multiple intrarticular injections, complication rates higher in younger patients and involving larger joints
Kendall, 1958 (100)	Various forms of arthritis and tendinitis	2256	Various agents	Most common side effects reported were muscular weakness, nausea, vertigo, and allergic reactions	Overall incidence of adverse effects only 1.09%
LaRoche, 1990 (101)	OA and RA	2	Long-acting agents	Two patients developed bilateral osteonecrosis of the hips; 1 also developed bilateral humeral head osteonecrosis	Multiple intrarticular injections
Leadbetter, 1995 (2)	Knee arthritis	1	Triamcinalone hexacetonide	Serum glucose to 300 mg/dL and serum WBC of 20,000/mm^3	Intra-articular injection
Roseff et al. 1984 (102)	Musculoskeletal pain	1	Various agents	Osteonecrosis of the femur	Multiple soft tissue injections over 18 y

posttreatment follow-up periods that prevent the discovery of longer-term complications, the true incidence of complications is likely underreported due to an underestimation of the numerator (true number of complications). Similarly, the studies that focus on complications of such treatment (Table 2, group B) actually overreport the true incidence of complications due to an underestimation of the denominator (number of subjects exposed).

The severity and types of complications reported differed substantially between the two Table 2 study type groups. Group A studies reported relatively few, mostly minor complications, and group B listed numerous, often serious complications. Postinjection site pain was a commonly reported complication in group A subjects. If postinjection site pain is excluded from consideration as a true complication, the incidence of complications in this group decreases from 15.2% to 5.5%. The complication rate of group B studies was 100%. The true total and specific complication incidences due to corticosteroid injection therapy are likely between the rates of the 2 groups. Future prospective studies are required to provide specific complication incidence data.

Although numerous articles report tendon ruptures following corticosteroid injection treatment of various athletic injuries, it is not possible to prove causation. Instead, it is possible that the underlying tendon pathology that prompted such therapy may have been the cause of or at least may have contributed to tendon rupture. The review also identified that many cases of tendon rupture occurred after an individual received multiple injections to a particular site. This may suggest, but does not prove, that a greater number of injections to a site predispose to complications such as tendon rupture. Various authors have written opinions on what constitutes a safe maximal number of corticosteroid injections. Among these are that the maximum number of injections administered should be 5 at 2-week intervals for lateral epicondylitis,[47] 4 to a single site,[18,48] and 3 at 2-week intervals for subacromial bursitis.[49] Some authors caution that an injured structure that has been injected with corticosteroids should be rested and protected for a minimum of 10 days following injection.[50–52] However, it should be emphasized that the medical literature does not provide clear evidence as to what constitutes a safe maximum number of corticosteroid injections.

Although several studies examined the efficacy of nonsteroidal anti-inflammatory drugs in the treatment of acute athletic injuries,[53–58] no studies similarly investigated the efficacy or complications of systemic corticosteroid therapy. Oral corticosteroids administered as a steroid burst, in which an initial high dose is tapered rapidly over 5 to 14 days, is a common treatment prescribed for various acute inflammatory conditions such as asthma flare, plant dermatitis, and acute allergic disorders. Table 6 summarizes reports of the complications of long-term ($\geq$14 days) and short-term ($<$14 days) systemic corticosteroid therapy in humans for various nonathletic injury medical conditions. The 13 studies that report complications of long-term therapy provide little information that usefully contributes to the formulation of appropriate guidelines for the use of short-term systemic corticosteroids for treating athletic injuries. Of the 7 studies reporting complications that occurred following short-term systemic corticosteroid therapy, only 2 provide information that may help eventually establish such guidelines: (1) the case of a young male runner who received a short course of prednisone and developed a tibial stress fracture,[59] and (2) 3 subjects who developed multifocal osteonecrosis after short-term, high-dose systemic corticosteroid treatment.[60]

Questions not answered by this review include the following: (1) the true incidence of complications of corticosteroid injections in the treatment of athletic injuries,

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TABLE 6. Complications of Long-Term and Short-Term Systemic Corticosteroid Treatment in Humans

Investigation (Reference)	Subjects	Intervention	Design	Dependent Variables	Results
Long-term treatment+A12					
Abuekteish et al, 1995 (32)	4 asthmatic children and young adults taking inhaled CS and having received long-term (>4 wk) or frequent short courses of oral CS	Inhaled CS plus long-term or frequent courses of oral CS	Retrospective	Slip-lamp ophthalmoscopic examinations for the presence of subcapsular cataracts	One girl who had taken several prolonged courses of oral CS was identified with posterior subcapsular cataracts
Alarcon et al, 1994 (103)	1 subject with feigned bronchial asthma	Long-term oral and inhaled CS therapy	Retrospective	Development of osteonecrosis of the femur	Factitious disorder resulting in osteonecrosis of the femur associated with CS use in feigned bronchial asthma
Dasgupta et al, 1991 (104)	16 subjects with polymyalgia rheumatica (PMR)	IM injections of 120 mg depo-methylpred-nisolone q 3 wk to induce and then maintain disease remission	Prospective	Development of adverse effects associated with CS	Multiple adverse effects identified, in proportion to the CS doses administered
Jones et al, 1996 (105)	44 dialysis patients with end-stage renal disease	Systemic CS	Retrospective	Spontaneous tendon ruptures	Subjects were more likely to sustain tendon ruptures associated with extended CS use
Lauzon et al, 1987 (106)	1 patient with seropositive rheumatoid arthritis	Long-term oral CS	Retrospective	Spontaneous tendon ruptures	Multiple tendon ruptures around large weight-bearing joints
Mertens et al, 1995 (107)	111 patients with PMR or temporal arteritis	High-dose CS	Retrospective	Development of adverse effects associated with CS	Vertebral compression fractures, 10 (9%) patients
Naiker et al, 1993 (108)	69 renal transplant recipients	Long-term oral CS	Retrospective	Development of avascular necrosis (AVN) as diagnosed by x-rays or bone scans	AVN developed in 14 (20.2%) subjects with a mean onset 19 mo posttransplantation; those with the highest risks for AVN: Indian ethnicity, cadaver transplants, frequent rejection bouts, frequent other steroid side effects, alcohol use, and osteoporosis
Petri, 1995 (109)	407 patients with SLE	Long-term oral CS	Retrospective	Development of musculoskeletal side effects	Avascular necrosis is the most common complication of SLE over time and correlates with CS dosages
Prensky et al. 1984 (110)	8 patients with familial progressive polyneuropathy	Methyl-prednisolone 45-60 mg/m2 or placebo	Double-blind, crossover	Development of adverse effects associated with CS	A high incidence of complications possibly due to CS therapy, including weight gain, vertebral compression fractures, cord compression from enlarged nerve roots, myopathy, pseudotumor cerebri, and psychiatric disturbances
Pritchard et al, 1989 (111)	180 patients with hand-deforming SLE over 10 y	Long-term oral CS	Retrospective	Patellar tendon rupture associated with CS	4 subjects (2.2%) developed patellar tendon rupture; each subject had been on oral CS for >7 y
Thomas, 1984 (112)	100 elderly patients (76 with COPD, 19 with RA, 5 with UC)	Long-term CS therapy	Retrospective	Development of adverse effects associated with CS	40% of subjects experienced side effects; osteoporosis (16%) and hypertension (12%) were most common
Wilkinson et al, 1981 (113)	1 young female patient with progressively severely deforming seronegative arthritis and vasculitis	Long-term CS therapy	Retrospective	Development of spontaneous patellar tendon avulsions	Authors postulate that combination of high dose oral CS plus tendon damage by vasculitis caused tendon avulsions

(*continued on next page*)

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TABLE 6. (*Continued*) Complications of Long-Term and Short-Term Systemic Corticosteroid Treatment in Humans

Investigation (Reference)	Subjects	Intervention	Design	Dependent Variables	Results
Zonana-Nacach et al, 2000 (114)	539 SLE patients receiving long-term prednisone	Long-term oral CS	Retrospective	Risk of side effects associated with high-dose CS therapy	Increase in cumulative prednisone dose risks of osteoporotic fracture, CAD, cataracts, and avascular necrosis
Short-term treatment+A8					
Abuekteish et al, 1995 (32)	103 asthmatic children and young adults taking inhaled CS with or without occasional courses of short-term oral CS	Inhaled CS alone or with short-term burst(s) of oral CS	Retrospective	Slip-lamp ophthalmoscopic examinations	No cataracts identified
Dunlap et al, 1984 (115)	Review of complications associated with short-term CS in the treatment of asthma	Short-term CS	Review	Development of adverse effects associated with CS	Hyperglycemia and psychosis most common
Groff et al, 1990 (116)	Acute gout attacks	Short-term oral prednisone (30–50 mg/d initially) tapers over 10 days	Prospective	Development of adverse effects associated with CS	Only rare, mild complications reported and no rebound arthropathy
Sambrook et al, 1984 (117)	66 patients who underwent neurosurgical surgery to treat intracranial aneurysms	Short-term, high-dose CS postoperatively to prevent cerebral edema	Retrospective	Development of osteonecrosis	Of 44 patients available for follow-up a mean of 50 mo postoperatively; 1 patient developed bilateral osteonecrosis of the hips
Scaggs, 1986 (59)	A young male runner who received a short course of prednisone	Short course of prednisone	Retrospective	Development of a tibial stress fracture	Impossible to prove association between the stress fracture and the CS
Taylor, 1984 (60)	3 subjects who developed multifocal osteonecrosis afer treatment with short-term high-dose systemic CS	Short-term, high-dose CS	Case reports	Development of multifocal avascular necrosis	3 cases of multifocal osteonecrosis reported; each patient required THRs; 2 also had shoulder involvement; authors found 4 previous case reports of multifocal osteonecrosis after short-term, high-dose CS in the literature
Vincent, 1995 (118)	Review of neuropsychiatric complications in patients receiving CS therapy for various conditions	Short-term vs. long-term CS	Review	Development of adverse neuropsychiatric effects associated with CS	Neuropsychiatric complications are more common and severe with long-term CS but also occur with short-term CS

(2) comparative risks of single versus multiple corticosteroid injections, (3) comparative risks of intratendinous versus peritendinous corticosteroid injections, (4) appropriate safe intervals between repeated corticosteroid injection, (5) appropriate duration of rest time following corticosteroid injections before return to strenuous physical activity, (6) relative risks of tissue damage caused by the needle used to inject the corticosteroid agent versus the agent itself, (7) relative risks of long-acting versus short-acting corticosteroid agents, and (8) efficacy and complications of systemic corticosteroid therapy in the treatment of athletic injuries.

CONCLUSIONS

This critical review demonstrates that the existing medical literature does not provide precise estimates for complication rates following the therapeutic use of injected or systemic corticosteroids in the treatment of athletic injuries. Tendon and fascial ruptures are often reported complications of injected corticosteroids, whereas tibial stress fractures and multifocal osteonecrosis were among the most serious complications described with systemic corticosteroids.

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