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Anabolic Steroids and Tendons: A Review of their Mechanical, Structural and Biologic Effects

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Abstract

One of the suspected deleterious effects of androgenic-anabolic steroids (AAS) is the increased risk for tendon rupture. However, investigations to date have produced inconsistent results and it is still unclear how AAS influence tendons. A systematic review of the literature was conducted to identify studies that have investigated the mechanical, structural or biologic effects that AAS have on tendons. In total, 18 highly heterogeneous studies were identified. Small animal studies made up the vast majority of published research, and contradictory results were reported frequently. All of the included studies focused on the potential deleterious effects that AAS have on tendon, which is striking given the recent use of AAS in patients following tendon injury. Rather than providing strong evidence for or against the use of AAS, this review highlights the need for additional research. Future studies investigating the use of AAS as a possible treatment for tendon injury/pathology are supported by reports suggesting that AAS may counteract the irreparable structural/functional changes that occur in the musculotendinous unit following rotator cuff tears, as well as studies suggesting that the purported deleterious effects on tendon may be transient. Other possible areas for future research are discussed in the context of key findings that may have implications for the therapeutic application of AAS.

Introduction

Androgenic-anabolic steroids (AAS) are synthetic testosterone derivatives that have a number of therapeutic applications. In addition to being used to treat hormonal disorders such as hypogonadism and hypercortisolism[1], AAS have anabolic effects that can be used to counteract the muscle wasting associated with a number of diseases[2], including chronic obstructive pulmonary disease[3], HIV[4-6] and muscular dystrophy.[7] AAS have also been studied in patients suffering from traumatic injury, such as spinal cord injury (SCI). Following SCI, patients experience rapid deconditioning that is similar to the volumetric bone and muscle loss that occurs after prolonged immobilization.[8-10] Early studies suggest that AAS may counteract these effects[11,12] and randomized clinical trials have already been initiated.[13]

A number of harmful side effects are associated with AAS, particularly when they are used at supraphysiologic doses. Reproductive infertility, cardiomyopathy, atrial fibrillation, and hepatic dysfunction are well-documented in the literature. {Hartgens:2004eqa} However, tendon rupture, which is also widely reported as a potential side effect of AAS[14], has received limited attention. To our knowledge, the last review to focus on AAS-induced tendon pathology was published in the early 90s, and no study has attempted to systematically aggregate the available literature.[15] This paper systematically reviews studies reporting on the mechanical, structural or biologic effects of AAS, discusses recent, ostensibly counterintuitive studies that are taking a second look at AAS as potential therapeutic agents for patients with tendon injury, and highlights areas for future research.

AAS - The basics

While originally developed to maximize anabolic activity[16], AAS, like their non-synthetic counterparts, have both anabolic and androgenic effects. AAS exert their effects via three common pathways. The primary pathway targets androgen receptors to induce the formation of a steroid-receptor complex in the cell nucleus. The complex stimulates protein synthesis and reduces protein catabolism by influencing the transcription of DNA.[17,18] An alternative pathway targets the enzyme 5-α-reductase to convert AAS into dihydrotestosterone (DHT). DHT is a more active version of its AAS precursor and binds with a high affinity to androgen receptors.[19] However, organ systems with high 5-α-reductase activity are generally male accessory sex glands, while organs such as the heart and skeletal muscle possess low 5-α-reductase activity and exert a stronger anabolic response. Consequently, this secondary pathway is thought to play a larger role in promoting the androgenic effects of AAS.[20] Another alternative pathway targets the enzyme aromatase to covert AAS into the female sex hormones estradiol and estrogen. Aromatase plays a limited role under normal circumstances and is only activated when the androgen receptor is saturated.{Hartgens:2004eqa}

When considering the possible effects that steroids have on tendon, it is important to clearly distinguish AAS from corticosteroids. Unlike AAS, which have received little attention for their potential effects on tendon, corticosteroids are among the most commonly used treatments for tendinopathies.[21,22] Preclinical studies have linked corticosteroids to transient weakening of both intact and injured rotator cuff tendons[23], as well as irreversible damage to healing muscle.[24] There is also a fairly well-established clinical association between tendon injury and concomitant administration of

corticosteroids and fluoroquinolone.[25] However, corticosteroids exert their effects through different molecular mechanisms than AAS, namely, by suppressing the genes that encode for inflammatory proteins and (at high concentrations) promoting anti-inflammatory gene transcription.[26] As such, corticosteroids are likely to have very different effects on tendon than AAS.

The use of anabolic steroids as performance enhancing drugs in athletics was first documented in the 1950s.[27,28] Since that time, only limited evidence to support their ability to enhance athletic performance has been demonstrated.[29] Nevertheless, AAS do seem to be capable of increasing muscle mass and strength under certain conditions in healthy adults.[30-32] Additionally, they are commonly abused by recreational users looking to achieve cosmetic improvements in their physique. Despite being added to the list of Schedule III Controlled Substances in 1990[33], it was recently estimated that as many as 4 million Americans have used AAS; roughly 1 million of which may have experienced AAS dependence at some point in their life.[34]

While the short-term side effects of AAS are generally mild and reversible, long-term, high-dose AAS use is associated with severe adverse effects, including irreversible cardiovascular disease.[35] AAS may also cause dose-dependent behavioral and psychiatric effects[36], though studies have reported large variability in symptom presentation.[37] In contrast to other commonly abused drugs, AAS do not trigger the rapid increase in dopamine that typically drives substance abuse behaviors.[38] However, individual dependence may be confounded by the perceived value of achieving improvements in muscle size and strength, and long-term high-dose administration may eventually impact the dopamine, serotonin, and opioid systems.[39]

Tendons - The Basics

The mechanical properties of tendons depend on their biomolecular composition, microstructure and micromechanics.[40] Tendons are unique in that they are comprised of relatively few cells.[41] The main structural component of tendons is type I collagen, which is a heterotrimer consisting of two α1 chains and one α2 chain.[42] Type I collagen gives tendons their high tensile strength[43], but the specific structure of tendon depends on the parallel organization of type I collagen fibrils rather than expression of type I collagen itself.[44]

Proteoglycans, which account for only a small fraction of the tendon's total dry weight[45], can indirectly influence tendon function though their regulation of collagen fibrillogenesis.[46] Although a detailed understanding of their function in tendon healing is lacking[47], proteoglycan interactions are known to modulate collagen fibril orientation[48] and increased levels of proteoglycans are a characteristic feature of tendinopathy.[44,49] It has also been suggested that accumulation of proteoglycan fragments within the extracellular matrix may contribute to age-related changes in the tensile properties of tendons and ligaments.[50]

The almost acellular, collagen I-rich structure of tendons limits their regenerative potential and poses major clinical challenges.[51] Acute tendon injury and chronic tendon pathology cause marked morbidity and often require surgical intervention[52], but the clinical options for treating tendon injuries are often unsatisfactory[41,53], especially in elderly populations.[54] Approximately 15% of the general population suffer from rotator cuff-related shoulder pain[55] and re-tear following arthroscopic rotator repair surgery

occurs frequently.[56,57] It has been estimated that between 30% and 50% of all sporting injuries involve tendons.[58]

Tendon healing is generally thought to occur in three overlapping phases: inflammatory, regenerative and remodeling.[59] The first 24 hours comprise the inflammatory phase, which is characterized by the migration of neutrophils and other inflammatory cells to the wound site.[48] The regenerative phase begins several days after injury and is characterized by cell proliferation[60] and synthesis of extracellular matrix (ECM) by fibroblasts.[61] The remodeling phase, which begins 6–8 weeks after injury and can last as long as a year[59], is characterized by reduced cellularity, decreased type III collagen synthesis[48], and the eventual replacement of fibrous tissue with scar-like tendon tissue.[62]

Cytokines and growth factors, released following injury by tenocytes and leukocytes, are closely involved in the repair response.[47] For example, TGF-β, a collagen stimulating growth factor, is known to play a major role in the genesis of tendons and ligaments. TGF-β transiently attracts fibroblasts to the wound site[63] and is a potent inducer of tendon markers in mesenchymal cells.[64] Fibroblast growth factors (FGFs), which play a role in angiogenesis and mitogenesis by facilitating collagen synthesis and turnover, are also important in tendon healing. Deficiencies in the FGF family correlate with higher susceptibility to rotator cuff tears[65] and the level of FGF-2 and its receptors are increased during the first week following injury.[66]

The Matrix Metalloproteinases (MMPs) are another important biological mediator involved in the repair and homeostasis of tendon. MMPs are a family of zinc-dependent proteases that cleave intact fibrillar collagen by hydrolyzing ECM components[67,68] and

altering the biological functions of ECM macromolecules.[69] A multitude of MMPs are thought to play a role in tendon degradation, including MMP-1, MMP-8, and MMP-13.[70,71] Doxycycline-mediated inhibition of MMP-13 has been used to improve rotator cuff repair and rotator cuff tears are correlated with decreased levels of tissue inhibitors of metalloproteinases (TIMPs).[72]

In addition to the biological mediators themselves, alterations in the mechanical environment are known influence tendons directly, as well as by modulating the expression of extracellular matrix proteins, growth factors, transcription factors, and cytokines.[73] For example, the gradual and temporary loss of tensile loading is associated with decreased scleraxis (Scx) expression[74], a transcription factor specific to tenocytes and their progenitors, while excessive mechanical loading is capable of inducing differentiation of tendon stem cells and is associated with degenerative tendinopathy.[75] Physical loading also influences the expression of both tenomodulin and type I collagen[76,77], and appears to induce morphological, mechanical and biochemical changes in tendon.[78]

Methods

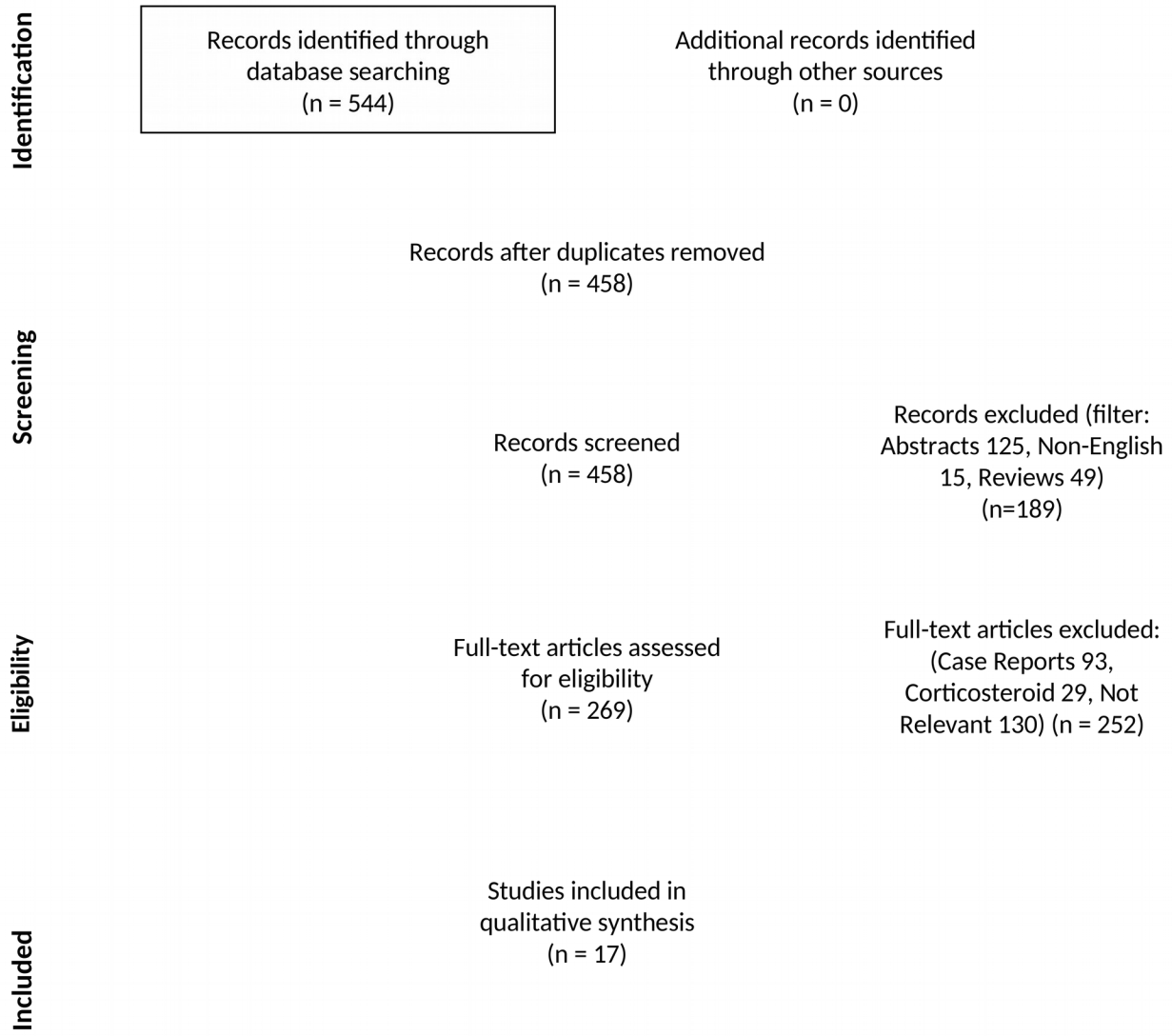

Figure 1: PRISMA flowchart. Methodology for systematic review of the literature.

Identification of Studies

The methodologic approach for this study was based on items 1-11c of the PRISMA (Preferred Reporting Items and Systematic Reviews and Meta-Analyses) checklist.[79] In keeping with our aim of providing a comprehensive overview of the available literature rather than summary or aggregation of data from individual studies, PRISMA items pertaining to the collection and synthesis of data were not utilized (11a-17). PubMed, MEDLINE, and the Cochrane Library databases, were independently reviewed by two authors (R.T. and I.J.) on January 2018 using the search terms “rotator cuff tears steroid”, “tendon anabolic steroid”, and “steroid tendon rupture”. **(Figure 1)**. The preliminary screen identified 544 articles. After excluding 86 duplicates and screening 458 articles, 269 full text articles in English were considered. Of the 269 eligible articles, there were 93 articles involving case reports, 29 articles using corticosteroids, and 130 articles that were not relevant to this review. A total of 18 articles were available for a systematic review.

Data collection

Full-length articles published in English that investigated the mechanical, structural and/or biologic effects of AAS were considered for inclusion. *In vitro* studies, *in vivo* studies and clinical studies (excluding case reports) were considered for inclusion. Basic descriptive data was extracted, including treatment variables, follow-up time, study groups, and sample size. Major findings (or a lack thereof) were generalized and organized to provide high-level overview of the literature.

201

Results

Study type	Study	Study Description	Study Model	Tendon Group	Drug	Rout	Dose	Frequency	F/U time	Sample Size
Clinical Studies	Evans 1998[80]	Case Controlled Study: Steroid users vs non-users	Clinical	Distal biceps tendon	Test + Nan	IM	500mg Test + 400mg Nan; or 250mg Test + 400mg of Nan	Weekly	N/A	4 (2 participants per group)
	Seynnes, 2013[81]	Case Controlled Study: Steroid and/or exercise as variables	Clinical	Patellar	Unspecified	Unspecified	Unspecified	Unspecified	N/A	24 (8 participants per group)
Animal studies	Michna,1986[82]	Steroid and/or exercise as variables	Mice	Flexor digitorum longus tendon	Met	IM	3.2 mg/kg	Weekly	1 week or 10 weeks	20 (5 animals per group)
	Michna, 1987[83]	Steroid and/or exercise as variables	Mice	flexor digitorum longus tendon	Met	IM	3.2 mg/kg	Weekly	1 week or 10 weeks	20 (5 animals per group)
	Wood 1988[84]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	IM	16 mg/kg	Single injection	6 weeks	24 (6 animals per group)
	Karpakka 1992[85]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	IM	1mg/kg or 5mg/kg	Twice a week	1 week or 3 weeks	56 (6 animals per group)
	***Miles, 1992[86]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Stan followed by Nan	IM	10mg followed by 3mg/kg	Single, followed weekly injections	6 weeks	24 (6 animals per group)
	***Inhofe, 1995[87]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Stan followed by	IM	10 mg, followed by	Single, followed	6 weeks	48 (12 animals per

					Nan		3mg/kg	weekly injections	or 12 weeks	group)
	Marqueti 2006[88]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	Sub-Q	5mg/kg	Weekly	5 weeks	40 (10 animals per group)
	Marqueti, 2008[89]	Steroid and/or exercise as variables	Rats	Achilles and flexor tendons	Nan	Sub-Q	5 mg/kg	Twice a week	7 weeks	40 (10 animals per group)
	Marqueti 2011[90]	Steroid or exercise as variables	Rats	Achilles Tendon	Nan	Sub-Q	5mg/kg	Twice a week	7 weeks	24 (6 animals per group)
	Marqueti 2012[91]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	Sub-Q	5mg/kg	Twice a week	7 weeks	24 (6 animals per group)
	Marqueti 2014[92]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	Sub-Q	5mg/kg	Twice a week	7 weeks	20 (5 animals per group)
	Tsitsilonis 2014[93]	Steroid and/or exercise as variables	Rats	Achilles Tendon	Nan	IM	5mg/kg	Twice a week	12 weeks	24 (6 animals per group)
	Papaspiliopoulos, 2010[94]	Steroid and/or immobilization as variables	Rabbit	Rotator cuff	Nan	IM	10 mg/kg	Single application	15 days	48 (12 animals/group)
	Wieser 2015[95]	Steroid or insulin-like growth factor vs. control	Sheep	Rotator cuff	Nan	IM	150 mg	Biweekly	6 weeks	20 (7 control, 7 steroid, 6 IGF)
In vitro studies	Triantafillopoulos, 2004[96]	Bioartificial tendons were treated with steroid and/or loading as variables	Human	Rotator cuff (Supraspinatus tendon)	Nan	Direct	100 nM (equivalent to FDA-approved dose)	Single application	7 days	6 subjects (3 tendons per subject)

	Denaro, 2010[97]	Tendon culture treated with low- and high-dose, representing physiologic and super-physiologic doses, respectfully	Human	Rotator cuff (Supraspinatus tendon)	DHT	Direct	10^{-9}M or 10^{-7} M	Single application	96 hours	3 subjects

Table 1: Overview of Included Studies. *** indicates highly influential studies, Nan = Nandrolone decanoate, Test = Testosterone, Stan = Stanozolol, Met = Methandienone, DHT = Dihydrotestosterone.

In total, 18 studies were included in this review (**Table 1**). While methodological heterogeneity precludes quantitative synthesis of the available data, some general trends do emerge. Small animal studies made up the vast majority of published research, with most groups injecting supraphysiologic doses of nandrolone decanoate (corresponding to the commonly prescribed dose in humans). Achilles tendons in rats were studied the most commonly (10 studies). Only a few studies have investigated the effects of “stacking”, which refers to taking of two or more anabolic steroids at the same time (a common practice among AAS abusers[98]), and no studies have investigated the effects of orally administered AAS on tendon, despite the fact that oral preparations are already being investigated clinically as an aid to post-operative recovery and rehabilitation in patients following rotator repair surgery.[99]

The following sections discuss the potential mechanical, structural and biologic effects that AAS have on tendon (**Table 2**). Overall, the available data as a whole is insufficient to support or oppose clinical decision making.

Effect type	Study type	Effect description
Mechanical Effects	Clinical	Potentially deleterious biomechanical effects[81]
	Animal	Potentially deleterious biomechanical effects when combined with exercise[86,87,93]
		AAS-associated biomechanical effects were unremarkable[84]
		Potentially deleterious biomechanical effects[90]
	In Vitro	Potentially beneficial biomechanical effects[96]
Structural Effects	Clinical	Ultrastructural changes in collagen fibers were not observed[80,81]
	Animal	Potentially deleterious ultrastructural changes in collagen fibers[82-84,86,88,93]
		Ultrastructural changes in collagen fibers were not observed[87,95]
		Increased cellularity and vascularity[92]
	In Vitro	Potentially beneficial ultrastructural changes in collagen fibers[96]
Biological Effects	Animal	May negatively affect tendon homeostasis[85,88,89,91,92]
		Reduced MMP-2[89,91]
		No change in type III collagen or fibronectin[87]
	In Vitro	Increased MMP-3[96]
		Tendinocyte proliferation and dedifferentiation[97]

Table 2: Mechanical, Structural and Biologic Effects of AAS on Tendon.

Biomechanical effects

The notion that anabolic steroids predispose tendon to rupture by altering their biomechanical properties seems to be largely based on case reports and a handful of highly influential animal studies published in the late 80s and early 90s. One of the first of these early studies was published by Miles et al.[86] Miles' group found that a stacked

anabolic regimen for 6 weeks in combination with physical training increased Achilles tendon stiffness in rats, which caused the tendons to fail with less elongation. While the AAS regimen didn't result in significant differences in the ultimate force at failure, the energy at the time when the tendon failed, toe-limit elongation, and the elongation at the time of the first failure were all significantly affected. A similar study published several years later by Inhofe et al generally supported these findings.[87] Rats were given stanozolol followed by weekly injections of nandrolone decanoate for 6 weeks and animals were euthanized at either 6 or 12 weeks. Differences in the elongation to first failure, energy to first failure and stiffness after 6 weeks were observed. However, Inhofe's group didn't find differences between the AAS-treated animals and controls at week-12, which has potentially important implications for clinical translation, as it suggests that the short-term biomechanical effects of AAS may be reversible.

Recent investigations using unstacked AAS regimens have generally supported early accounts that AAS reduce tendon elasticity. For example, Marqueti et al reported lower elasticity and capacity to resist load in certain regions of various tendons following bi-weekly injections of nandrolone decanoate[90] and Seynnes et al reported increased patellar tendon stiffness and higher tensile modulus in trained individuals that had abused AAS compared with non-steroid users.[81] While some studies have reported beneficial biomechanical effects[94,96], the literature overall supports the supposition that (under certain circumstances) AAS can increase tendon stiffness. However, as others have pointed out[33], a distinction should be made between loss of elasticity and actual tendon rupture.

Structural effects

The structural effects of AAS on tendon are not well understood and conflicting reports have been published. Early studies by Michna et al found time-dependent collagen dysplasia, qualitative changes in the organization of tendon collagen fibrils, and dramatic ultrastructural anomalies in the texture of individual fibrils after 3.2 mg/kg methandienone was administered to mice for 10 weeks.[83] A year later, Wood et al published a report showing that administrations of AAS increased crimp angles and decreased collagen fibril length, particularly when the use of AAS was combined with physical exercise. [84] However, findings published the same year by Evans et al[80], as well as the later studies by Miles et al[86] and Inhofe et al[87], called the generalizability of these early findings into question. Miles group noted a trend toward increased collagen fibril size using electron microscopy, but only when steroid was combined with exercise, and Inhofe's group did not observe significant changes using either light microscopy or electron microscopy.

No consistent AAS-induced ultrastructural alterations have been found to account for the reported changes in biomechanical properties, and more recent studies have further added to the confusion.[88,92,93,95-97] In their 2004 paper, Triantafillopoulos et al suggested that cross-linking be investigated as a possible mechanism behind the changes attributed to exercise and anabolic steroid administration[96], but no studies have reported on AAS-induced cross-linking to date. Moreover, only two human studies evaluating the potential structural differences between the tendons of AAS users and non-users has been published. The first of these studies used light and electron microscopy to evaluate ruptured distal biceps tendons that had been biopsied during surgical repair of AAS users vs non-users.[80] No difference in collagen fibril ultrastructure

was observed, leading the authors to conclude that anabolic steroids may not induce ultrastructural collagen changes in humans. However, their study design and small sample size (n= 4) limits firm conclusions, and the extreme AAS doses taken by their subjects limits the comparability of their findings to pre-clinical models. The second clinical study compared the cross-sectional area (CSA) of trained AAS abusers to trained and untrained individuals that had not used AAS previously.[81] When normalized to quadriceps maximal isometric torque, CSA was similarly reduced in both trained groups. However, the authors were careful to point out that maximal tendon stress was considerably higher in the trained group that had taken steroids, which suggests that tendon hypertrophy in AAS users may be insufficient to meet the increased demands. However, because dosing was not specified, it is difficult to draw meaningful conclusions.

Biological effects

One of the early studies to look at the biological effects of AAS on tendon measured the activities of prolyl-4-hydroxylase and galactosyl hydroxylysine glucosyltransferase to estimate the rate of collagen synthesis.[85] Rats were given high- or low-dose (1mg/kg or 5mg/kg, respectfully) intramuscular injections of nandrolone decanoate twice a week for 1 or 3 weeks. The activity of prolyl-4-hydroxylase and the concentration of hydroxyproline decreased significantly in the high-dose cohort after 3 weeks of treatment, indicating a decrease in collagen biosynthesis in tendon. More recent reports have also suggested that AAS negatively affect collagen metabolism in tendon.[91,92]

Given their involvement in ECM degradation and tissue remodeling, a number of studies have investigated the relationship between AAS and Matrix metalloproteinases (MMPs). In a series of papers published by Marcheti et al, a supraphysiological dose (5mg/kg) of nandrolone decanoate was shown to abolish the MMP activity associated with physical training[88], cause tendon/region-specific decreases in MMP-2 concentration[89], and cause potentially harmful effects on ECM remodeling.[91] Marqueti's findings are particularly interesting because they stand in sharp contrast to those reported earlier by Triantafillopoulos et al.[96] Using bioartificial rotator cuff tendons[100], Triantafillopolous group found that the combination of loading and AAS significantly enhanced tissue remodeling. However, Triantafillopolous' group also found that AAS-treated tendons demonstrated improved flexibility, deformability, and ultimate stress-to-failure, as well absorbed more energy before failure. Triantafillopolous' findings are inconsistent with the majority of published research, which suggests that the bioartificial rotator cuff tendons may not accurately approximate *in vivo* conditions or that the effect of AAS on rotator cuff tendons may be very different than their effect on the Achilles tendon. The inconsistent response could also be due (at least in part) to the dose and availability of the drug, which Triantafillopolous reports as being 'equivalent to the dose recommend by FDA.'

Discussion

While rigorous studies linking AAS use to tendon rupture are still needed, the notion that supraphysiologic doses of AAS predispose tendon to rupture by reducing elasticity is widely reported in the literature. Two alternative (though not mutually exclusive) hypotheses are often invoked to explain AAS-associated tendon rupture.[33,89,101,102] The first hypothesis posits that AAS have little-to-no deleterious effect on tendons themselves. Instead, muscular hypertrophy, without corresponding strengthening of the associated tendons, explains tendon-associated rupture. The second hypothesis is that, at high doses, particularly in conjunction with physical exertion, AAS damage the structure of the tendons and makes them more vulnerable to rupture, even in the absence of excessive stress. This review demonstrates that neither hypothesis can be confirmed or denied based on the currently available evidence. Moreover, it is unclear how factors like stacking, dosing and exercise influence tendon stiffness.

While seemingly counterintuitive given association between AAS and tendon rupture, recent studies are investigating whether AAS provide therapeutic benefits to patients undergoing rotator cuff surgery. This approach is based on the notion that stimulating protein synthesis during a critical period following injury provides benefits that are outweighed by the potential short-term side-effects of AAS.[103] In normal rotator cuff tears, fatty infiltration and muscle atrophy have been shown influence disease progression[104,105], regenerative potential[106], and functional outcomes following surgical repair.[107] In an attempt to counteract these deleterious effects, Gerber et al administered nandrolone decanoate systemically (via injection into the quadriceps muscle) or semi-

locally (via injection into both the quadriceps and supraspinatus muscles) to rabbits following supraspinatus tendon release.[108] They found that AAS injections prevented fatty infiltration of the supraspinatus muscle and reduced functional muscle impairment. Interestingly, no differences were reported between the systemic and semi-local treatment groups. Overall, they concluded that AAS may diminish the irreparable structural and functional changes that occur in the musculotendinous unit as a result of chronic rotator cuff tears. However, the strength of their conclusion is weakened by the fact that they could not obtain sufficient biopsy material from the tendon for analysis.

Follow-up studies published by Gerber's group have generally supported their earlier findings in rabbits.[108] In sheep, weekly intramuscular injections of 150 mg nandrolone decanoate prevented degenerative muscle changes when they were administered at the time of injury, but not when administered at the time of surgical repair.[109] In addition to supporting earlier work, these findings have important clinical implications, as they suggest that the potential beneficial effects of AAS may strongly depend on how quickly they are administered following injury. In another similar study conducted by the same group, Fluck et al[110] looked at whether tendon release and myotendinous retraction caused alterations in lipid-related gene expression that lead to fatty infiltration. Compared to control animals, nandrolone administration starting immediately after tendon release prevented increases in the area percentage of fat and mitigated the reduction in the area percentage of muscle after tendon release. However, when nandrolone was administered starting at the time of repair, no changes in muscle volume or muscle composition were observed. Additionally, despite lowering the overall abundance of lipid species, nandrolone administration up-regulated the transcription of

factors involved in fat cell differentiation and lipid biogenesis. Similar to Gerber's first study[108], neither of these follow-up studies actually looked at the tendon. As such, their results only relate indirectly to tendon injury/pathology.

When considering the information presented in this review and the prospective outlook for continued research more broadly (**Table 3**), it is important to understand that our findings apply exclusively to the mechanical, structural or biologic effects that AAS have on tendons. However, as the studies by Gerber's group highlight, the overall clinical scenario relates to the muscle-tendon unit, not just the tendon itself. As such, the importance of the adjacent muscle, ligaments and enthesis should not be discounted. Unfortunately, with the exception of case reports, very little data on the tissue-specific effects of AAS (e.g. tendon vs muscle vs ligament) have been published. Of the studies included in this review, only Karpakka's study looked at both muscle and tendon.[85] While they did not observe a dose-dependent response in muscle, the concentration of prolyl 4-hydroxylase and hydroxyproline in the tendon decreased significantly in the group treated with high-dose (5 mg/kg) nandrolone decanoate. Despite the lack of clinical data looking at the effects of AAS on tendon, there is some data (albeit limited) that suggests that supraphysiologic testosterone supplementation may be a useful adjunct therapy for patients undergoing anterior cruciate ligament reconstruction.[111,112]

Key Findings that have Notable Implications for Continued Research and Future Clinical Translation
AAS have been shown to prevent long-term functional muscle impairment following traumatic tendon injury, but these effects are strongly dependent on how quickly they are administered

The potentially deleterious biomechanical effects of AAS may be transient	
Systemic and locally administered AAS may affect tendon similarly	
Potential Areas for Future Research	
Tendon Injury/Pathology	No studies to date have investigated the effects of AAS for tendinopathy or traumatic injury.
Dose-Response	Most studies to date have used high concentrations of AAS. Studies elucidating dose-response relationships are needed, particularly for lower doses
Drug-response	Most studies to date have used Nan, which has been discontinued. Studies investigating currently approved and more widely used formulations are needed.
Stacking	No studies have investigated the differences between stacked and unstacked regimens.
Administration Route	No studies have investigated how drug administration route influences drug response, and no preclinical data using oral formulations have been published to date.
Timing	For studies investigating AAS as a potential treatment, additional studies elucidating the ideal time course for administration are needed.
Response population	No studies have investigated how sex or age influences drug response
Tissue-Specific Effects	AAS are likely to affect tendon, muscle and the fibrocartilage enthesis differently, but no studies to date have been conducted to characterize these differences.

Table 3: Prospective outlook for continued research investigating the mechanical, structural or biologic effects that AAS have on tendons.

In addition to AAS, other anabolic agents are also being investigated for tendinous healing. A notable example is growth hormone (GH), which exerts anabolic effects directly, as well as through stimulation of insulin-like growth factor-I, insulin, and free fatty acids.[113,114] While claims that GH enhances physical performance are not generally supported by the scientific literature[115], some have suggested that their anabolic effects may provide benefits to patients with muscle and tendon injuries.[116] Several clinical studies have been published to date. A 2010 study in healthy men (n=10) found that administration of recombinant human GH stimulated matrix collagen synthesis in skeletal muscle and tendon.[114] However, a multicenter, prospective,

randomized, blinded exploratory trial investigating the use of growth hormone on rotator cuff healing after arthroscopic repair (n=50) failed to demonstrate statistically significant improvements in healing or outcomes.[117]

One of the major limitations of this review is the heterogeneity of the included studies, which precludes quantitative synthesis of the available data. While this approach allowed a comprehensive overview of the literature, important differences between studies should not be overlooked. For example, enhanced or reduced loading were regularly used as treatment variables, and several studies only found differences when AAS were combined with changes in physical loading.[86,87,93] There was also wide variability between type, dose, route, and administration frequency. Additionally, two of the most influential studies published to date are also the only studies to use stacked AAS regimens.[86,87] Lastly, over half of the studies included in this review were conducted on the Achilles tendons in rats. However, different tendons are subjected to different mechanical loads[118] and differences in the cellular/molecular microstructure can cause tendons (and tendon sub-regions) to respond differently to mechanical loading.[44] This suggest that there may be tendon-specific responses to AAS, AAS-associated increases in loading, or both.[89,90]

Conclusion:

Despite roughly 30 years of research, AAS-associated tendon pathology/injury is still poorly understood. While several studies have linked increased tendon stiffness to AAS use, the data is far from conclusive and a distinction should be made between loss

of elasticity and actual tendon rupture. Moreover, no consistent AAS-induced ultrastructural or biochemical alterations have been found to account for the changes in biomechanical properties, and the limited, often contradictory results preclude firm conclusions. Current research is taking a second look at AAS as potential therapeutic agents for patients with severe tendon injury. Despite being reasonably supported by reports indicating that AAS may counteract the irreparable structural/functional changes that occur in the musculotendinous unit following rotator cuff tears, no studies reporting on the structural, biological, or mechanical effects of AAS on tendon have investigated their use as potential therapeutic agents. Rather than providing strong evidence for or against the use of AAS, this review highlights the need for additional studies. Potential areas for future research include studies aimed at understanding dose- and drug-dependent responses. There is also reasonable evidence to support further studies investigating the use of AAS following rotator cuff injury, although no studies to date have explicitly shown that AAS have beneficial effects on the structural, biological, or mechanical properties of tendon. Other potential areas for future research include studies aimed at better understanding the effects of stacking and ultra-high treatment regimens, which are often used by recreational abusers.

Figure and Table Descriptions

Figure 1: PRISMA flowchart. Methodology for systematic review of the literature.

Table 1: Overview of Included Studies. *** indicates highly influential studies, Nan = Nandrolone decanoate, Test = Testosterone, Stan = Stanozolol, Met = Methandienone, DHT = Dihydrotestosterone.

Table 2: Mechanical, Structural and Biologic Effects of AAS on Tendon.

Table 3: Prospective outlook for continued research investigating the mechanical, structural or biologic effects that AAS have on tendons.

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