Anabolic Androgenic Steroids in Orthopaedic Surgery: Current Concepts and Clinical Applications

Alexander E. Weber, MD
Matthew C. Gallo, BA
Ioanna K. Bolia, MD, MS, PhD
Emmett J. Cleary, BS
Todd E. Schroeder, PhD
George F. Rick Hatch III, MD

ABSTRACT

Despite the well-documented effects of testosterone and its synthetic derivatives—collectively termed anabolic androgenic steroids (AASs)—on the musculoskeletal system, the therapeutic use of these agents has received limited investigation within the field of orthopaedic surgery. In the last 2 decades, preclinical and clinical research has started to identify promising applications of the short-term use of AASs in the perioperative period. There is evidence to suggest that AASs may improve postoperative recovery after anterior cruciate ligament reconstruction and total joint arthroplasty. In addition, AASs may augment the biological healing environment in specific clinical scenarios including muscle injury, fracture repair, and rotator cuff repair. Current literature fails to present strong evidence for or against the use of AASs in orthopaedics, but there is continuous research on this topic. The purpose of this study was to provide a comprehensive overview of the current status of AAS applications in orthopaedic surgery, with an emphasis on preclinical data, clinical studies, and future directions.

Anabolic androgenic steroids (AASs) are synthetic testosterone derivatives designed to maximize anabolic activity and minimize androgenic effects.1 AASs have gained considerable notoriety in the last half century, which is attributable to their illegal use in athletic competition.2,3 Despite their reputation, AASs have a number of therapeutic applications. The anabolic effects of AASs may play a significant role in the treatment of muscle wasting associated with severe burns and a wide spectrum of chronic diseases such as human immunodeficiency virus, cancer, renal failure, hepatic cirrhosis, pulmonary disease, and muscular dystrophy.4-10 AASs have also been studied in the context of prolonged immobilization after spinal cord injury, which is characterized by volumetric bone and muscle loss; preclinical studies have shown beneficial effects, and a clinical trial is underway to validate these promising findings.11-13

The use of AASs to counteract muscle and bone loss is supported by a growing body of evidence showing a positive effect of AASs on muscle mass, strength, and bone metabolism.14-17 The applications of AASs related...
to the field of orthopaedic surgery have been historically limited. A notable exception is the use of AASs in the treatment of osteoporosis, which has been studied more extensively.18-22 Although testosterone may be indicated for men with osteoporosis, other AASs have been studied as a possible alternative, particularly in women, due to the lower risk of virilizing side effects.23,24 The clinical results with the use of AAS as an adjunct therapy in osteoporosis remains a subject of inquiry in both the male and female population.24-27 AASs have mostly been evaluated at a relatively low dose and with long-term administration in studies on osteoporosis.4,24-28 Only in the last two decades has short-term administration of AAS received investigation in orthopaedics.

Orthopaedic injury and accompanying surgery are almost always associated with the development of disuse muscle atrophy, which lengthens recovery and delays return to full strength.29 Disuse atrophy has been linked to negative outcomes in common orthopaedic procedures including but not limited to anterior cruciate ligament (ACL) reconstruction, total knee arthroplasty (TKA), and lower extremity fracture repair.30-34 Recent evidence suggests that the anabolic effects of AASs in muscle may be an effective method to improve postoperative recovery after such procedures.35-37 For example, the anabolic environment induced by AAS may also improve biological healing in specific clinical scenarios including muscle injury, fracture repair, and rotator cuff repair.21,38-40 Although the degree of direct muscle and bone healing from AAS administration remains inconclusive, a recent series of preclinical experiments demonstrated that AASs may halt fatty infiltration and improve healing of a repaired rotator cuff.39-41 This application highlights the potential of AASs to address the underlying pathophysiology in one of the most common causes of musculoskeletal pain and disability.42,43

To our knowledge, the last review to focus on the therapeutic applications of AAS in orthopaedic surgery was published in 2004, which was before many recent studies on the short-term use of AAS.28 The purpose of this present review is to provide a summary of the current status of AAS applications in orthopaedic surgery, with an emphasis on preclinical data, clinical studies, and future directions.

**Mechanism of Action and Effects of Anabolic Androgenic Steroids on Musculoskeletal Tissues**

The physiologic effects of testosterone and AASs in the musculoskeletal system have been reviewed elsewhere and will not be discussed in detail.16,44-46 Briefly, AASs are synthetic testosterone derivates that were developed with the goals of increased androgenic potency, prolonged biologic activity, and, in some cases, oral bioavailability.28 Compared with testosterone, which has an anabolic: androgenic ratio of 1:1, oxandrolone, for example, has a ratio of 13:1.46 Although developed to maximize anabolic activity, all AASs have some androgenic effects and may result in virilizing side effects depending on the dose and duration of use.16

AASs are thought to exert their actions through several pathways.46 First, AASs bind cellular androgen receptors (ARs), which promotes gene transcription that increases protein synthesis and reduces catabolism.47 Second, AASs interfere with glucocorticoid receptor expression, which results in an antifibrotic effect.48 Third, AASs exert effects on the central nervous system—though not fully elucidated—that are reflected in the behavioral changes seen with AAS use.46 Finally, AASs may be converted into dihydrotestosterone by the enzyme 5-α-reductase; dihydrotestosterone binds with high affinity to ARs and plays a larger role in the unwanted androgenic effects of AASs.35,49

AASs have an important role in musculoskeletal tissue homeostasis and have been reported to influence the biology of muscle, bone, tendons, and ligaments.50-53 A concise summary is presented below.

**Effect of Anabolic Androgenic Steroids on Skeletal Muscles**

Testosterone induces anabolic activity directly in muscle through ARs present in myocytes.54,55 Indirectly, testosterone mediates muscle growth via increases in insulin-like growth factor 1 and growth hormone levels.44,55 It has also been shown to regulate the activity of immune, fibroblast, and myogenic precursor cells, which are all involved in muscle regeneration after injury.44,55 Preclinical studies in rodents with AR deletion, AR overexpression, and in castrated male rats have provided valuable insights on the importance of testosterone in the development and maintenance of muscle mass.56-58 These findings have been also been validated clinically: testosterone replacement has been shown to increase lean body mass and muscle mass in young men and in old men with androgen deficiency.15,17,59 Testosterone may also increase strength in a dose-dependent manner.15,60

**Effect of Anabolic Androgenic Steroids on Bone**

Testosterone is a key regulator of bone mass in males.44,61 Trabecular bone mass is mediated by the
direct effects of testosterone on AR on osteoblasts, which in turn control osteoclastic resorption.62,63 In contrast, AR deletion studies in rodents have found that testosterone acts through an indirect mechanism to regulate cortical bone.64 In clinical studies, lower testosterone in older men is associated with lower bone mineral density (BMD), whereas testosterone supplementation in older or hypogonadal men can increase BMD.65,66 In women, estrogen is the primary regulator of bone metabolism.44,61 However, a study found that postmenopausal women with higher circulating testosterone levels had higher BMD, suggesting a secondary role for testosterone in regulating female bone mass that may increase in importance with aging.67

**Effect of Anabolic Androgenic Steroids on Tendons**
A widely reported side effect of AAS use is an increased risk of tendon rupture.68,69 Two hypotheses are often described in the literature: (1) AASs have no direct effect on tendons but can induce muscular hypertrophy and increased muscle strength, without associated tendon strengthening, resulting in an increased risk for rupture, or (2) that AASs, in combination with physical exertion, have a deleterious effect on tendon structure and healing.28,69 Preclinical studies in rodents have suggested that AAS use may negatively affect collagen synthesis and matrix metalloproteinase activity, which are both involved in tendon repair and homeostasis.70,71 However, as a recent review noted, investigations to date have produced inconsistent results, and it is still unclear how AASs influence tendons.69

**Effect of Anabolic Androgenic Steroids on Ligaments**
The effect of testosterone on ligament homeostasis is poorly understood. Surgical ACL specimens from young men and women have revealed that the ACL expresses ARs in both sexes, which suggests that it is a testosterone-responsive tissue.53,72 Furthermore, small preclinical and clinical studies have found that testosterone levels correlate with ACL stiffness, signifying a possible role in remodeling and tensile strength.72-74 As other sex steroids, namely estrogen and progesterone, have been shown in vitro to influence proliferation of fibroblasts and collagen synthesis in the ACL, testosterone may function similarly, but this has not been demonstrated.75,76 Although more work is needed to characterize the pathways through which testosterone acts on ligaments, the influence of sex steroid hormones has been proposed as one possible explanation for the sex disparity in ACL injury risk.77

**Side Effects of Anabolic Androgenic Steroids**
The effects of AASs in other tissues contribute to their known side-effect profile, which has largely been established through observational studies and case reports of nonmedical AAS users.28,68,78,79 The side effects of AAS use are generally benign and reversible (eg, acne, gynecomastia, and testicular atrophy), but long-term high-dose use is associated with severe adverse effects including irreversible cardiovascular disease and hepatic dysfunction.80,81 AASs may also cause dose-dependent behavioral and psychiatric effects including euphoria and aggression; long-term administration may alter dopamine, serotonin, and opioid neurotransmitter levels.46,82 Side effects specific to women include hirsutism, voice deepening, male-pattern baldness, and menstrual abnormalities, some of which persist even after AAS discontinuation.83

In prospective clinical studies, AASs have demonstrated an acceptable safety profile. Short-term use of physiologic or supraphysiologic doses of AASs in men has not been associated with serious adverse effects on lipid levels, hepatic function, hemoglobin levels, or behavior/mood.15,84-88

**Orthopaedic Applications of Anabolic Androgenic Steroids**

**A. Augmented Biological Healing Environment**

**A1. Muscle Regeneration After Injury**
Muscle contusion and strain injuries comprise more than 90% of all sports-related injuries.89 Although skeletal muscle has a robust capacity for self-repair, the severity of injury may result in delayed healing or incomplete healing that is complicated by fibrosis.90,91 Injury severity may also positively correlated with the duration of functional disability.92 Preclinical studies have shown an association between testosterone and processes implicated in muscle regeneration.44. However, few studies have directly evaluated the effect of AASs on muscle regeneration, and the available evidence is conflicting.93 Ferry et al.94 examined the effects of nandrolone decanoate (ND) on the effects of the soleus and extensor digitorum longus muscles after myotoxic injection. The authors found that ND increased the mass of the soleus but had no effect on the extensor digitorum longus relative to controls.94 In a follow-up study, the
same group found that ND did not improve isometric contractile strength in either muscle at 21 days postinjury.95

In a rodent model of muscle contusion, Beiner et al.96 found that ND administration did not increase the force-producing capacity of the gastrocnemius at 7 or 14 days postinjury. Conversely, two other preclinical studies found that ND administration was able to increase muscle regeneration, which was evaluated based on the number and morphology of myofibers present.97,98

Differences in preclinical findings may be explained by a varying regenerative response to different modes of muscle injury (eg, toxin induced versus contusion), dose and duration of androgen supplementation, and the outcome variables. To date, no human studies have evaluated the role of androgens in promoting muscle regeneration. Additional preclinical and clinical studies will be needed to better define how testosterone and AASs modulate muscle regeneration and the dose and duration for which they should be given for potential clinical benefit.

A2. Fracture Repair
Failure of fracture healing occurs in up to 10% of all patients and often leads to significant patient morbidity and substantial socioeconomic costs.99 Despite the known effects of testosterone in skeletal homeostasis, the direct effect of testosterone and AAS on fracture healing has not been well defined.44 Tarsoly et al.38 were the first to study this in 1979, showing that hypophysectomized (ie, lacking pituitary) rats had impaired callus formation but that this effect could be attenuated with testosterone supplementation. In another rodent study, Frankle et al. compared callus formation in rats with humeral osteotomies that were treated with weekly testosterone or methenolone enanthate, which has a high anabolic:androgenic ratio.100 The authors found that by 4 weeks, the calcium composition of the callus was similar between rats treated with testosterone or methenolone enanthate, with both groups having significantly more calcium than controls.100 Somewhat surprisingly, biomechanical testing and histology did not reveal a significant difference between the three groups at any time point (up to 6 weeks postinjury).100

It should be noted that the two studies referenced above involve systemic administration of testosterone or AAS.38,100 More recent animal studies have also shown that local administration of testosterone—in the form of a testosterone loaded scaffold material—can heal critical-sized long bone defects that would otherwise not heal.101-103 Although these studies suggest that testosterone is effective in fracture repair, only one study to date has evaluated its efficacy.104 Cheng et al.104 compared locally delivered testosterone and recombinant human bone morphogenetic protein 2 (rhBMP-2) for healing critical-sized femoral defects in mice. Micro-CT analysis of callus formation and bone regeneration as well as histological examination of trabecular and cortical bone found that found that testosterone was as effective as rhBMP-2 in fracture healing.104 RhBMP-2 is FDA approved for use in the treatment of open tibial fracture and anterior spinal fusion but is expensive and is associated with a number of adverse effects.105 Therefore, the authors concluded that testosterone may represent an effective, cost-effective osteoinductive stimulus for fracture healing.104 Future studies should seek to validate these preliminary findings in larger animal models of clinically relevant scenarios of bone loss such as fracture nonunion, revision total joint arthroplasty, and pseudarthrosis of the spine.

A3. Rotator Cuff Repair
Rotator cuff tears are one of the most common causes of musculoskeletal pain and disability and impose significant personal and societal costs.42,43 Despite advances in surgical techniques, incomplete healing and retears are common postoperative complications, with retear rates of up to 40% for small and medium tears and more than 90% in large or chronic tears.106,107 Incomplete healing and retears impose additional burden on patients and contributes to inferior outcomes.108 Therefore, there is an urgent need to improve rotator cuff healing rates. The biological hallmarks of a torn rotator cuff are muscle atrophy, fatty infiltration, and intercellular fibrosis of the muscle-tendon unit and are important prognostic factors for treatment.109-112 Recent studies with AASs have tried to address this underlying pathophysiology. Preliminary studies evaluating the effects of AASs on isolated rotator cuff tendon produced contradictory findings on the protective or detrimental role of AASs.70,113-117 The results of the study by Triantafillopoulos et al.,113 in particular, should be interpreted with caution as their group used a bioartificial tendon that produced results inconsistent with much of the available literature. However, a series of experiments involving the rotator cuff musculotendinous unit—not just the tendon itself—have provided valuable new insights on the potential role of AASs to improve rotator cuff healing.39,41,109

In the first experiment, Gerber et al.109 released the infraspinatus tendon in six sheep and monitored muscular changes for 40 weeks with CT, histology, and
electron microscopy. They found significant fatty infiltration, increased interstitial connective tissue, and a sevenfold decrease in elasticity relative to controls. These physiologic changes initially worsened after repair but, importantly, never improved to prerepair values. Building off this work, this group next performed a pharmacologic intervention study in a rabbit model of rotator cuff tear: when ND was administered (systemically and/or locally) at the time of supraspinatus release, these animals demonstrated significantly less supraspinatus retraction and no fatty infiltration compared with controls with supraspinatus release alone. This was the first work to show partial prevention of musculotendinous changes after rotator cuff release using AASs.

In a separate experiment, the same group found that AAS administration did not contribute to muscle regeneration in a sheep model of a chronic rotator cuff tear. Taken together with the previous study, this suggests that AASs may be effective in preventing degenerative muscle changes in the rotator cuff but are not regenerative. Most recently, the authors showed that AASs given at the time of a rotator cuff repair can prevent additional muscle atrophy but not fatty infiltration, which suggests that the beneficial effects of AASs may depend on how quickly they are administered after rotator cuff injury. The translational potential of these findings is currently under investigation: an ongoing randomized controlled trial (RCT) at the University of Southern California aims to examine the potential role of oral oxandrolone to facilitate healing of repaired rotator cuff tendons and to improve the functional outcomes in patients with chronic, degenerative rotator cuff tears who undergo arthroscopic repair (NCT03091075).

B. Improved Postoperative Recovery

B1. Hip Fracture Repair

Hip fractures are a common cause of morbidity and mortality in older people. It is estimated that up to 50% of women and nearly 25% of men are at risk for an osteoporotic fracture in their lifetime. These patients tend to be frail and undernourished and may have poor mobility at baseline related to reduced muscle mass and strength. Despite surgery and rehabilitation, many patients experience a further decline in mobility and function, which has significant personal and societal costs. Early mobility has been found to be predictive of improved outcomes. As AASs have had positive effects in treating other catabolic states, it is plausible that AASs may improve perioperative recovery and outcomes in the hip fracture population.

Although the overall quality of the evidence is low, a few small RCTs have provided mixed results on the effect of AAS on functional outcome after hip fracture repair in older patients (Table 1). In a pilot trial of 31 frail elderly females (mean age 82 years), Sloan et al. found no difference in the number of patients upgraded to a higher level of care, deaths, time to independent mobilization, or incidence of adverse events between patients who received postoperative nandrolone injections (weekly for up to 4 weeks) and those receiving placebo. A different study randomized 23 patients (aged >60 years) recovering from hip fracture surgery, and administered varied doses of AASs dependent on sex, and measured blood testosterone concentration. The authors noted no significant differences in knee extension strength between the AAS group and placebo at the final (14 weeks) follow-up. In another trial of 40 lean elderly women, Tidermark et al. compared AAS injections every 3 weeks for 6 months and daily protein supplementation compared with protein supplementation alone. The authors found some evidence, albeit weak, that AAS use was associated with positive effect on lean body mass and patient-reported function and quality of life. In a post hoc analysis of the same trial, Tengstrand et al. found that AASs did not seem to have any additional effect on BMD measured by dual-energy X-ray absorptiometry (DEXA) scan compared with protein-rich supplementation alone.

In contrast, a separate trial in elderly women (mean age 80.5 years) found that AAS injections every 3 weeks for 1 year and daily supplementation with vitamin D and calcium were associated with higher BMD, gait speed, and Harris Hip Scores after hip fracture compared with supplementation with calcium alone. While the dose and frequency of ND injections in this trial was the same as those in Tidermark, the differences in duration (1 year versus 6 months, respectively), and nutritional supplementation (calcium and vitamin D versus protein, respectively) makes it difficult to directly compare the results of these studies.

Overall, the small size and heterogeneous study designs of current trials provide insufficient data to draw conclusions on the effects of AASs on functional outcomes after hip surgery. As a recent Cochrane review notes, “Given that the available data points to the potential for more promising outcomes with a combined anabolic steroid and nutritional supplement intervention, we suggest that future research should focus on evaluating this combination.”

B3. Anterior Cruciate Ligament Reconstruction

Testosterone may serve a role in ligament homeostasis and strength, as discussed previously. However,
| Study                          | Level of Evidence | Type of Surgical Procedure | Study Design | Participants | Intervention                                                                 | AAS Administration Route | AAS Dose                | Duration of AAS Administration | Latest Postoperative Follow-up Time |
|-------------------------------|-------------------|-----------------------------|--------------|--------------|-------------------------------------------------------------------------------|--------------------------|-------------------------|-------------------------------|-----------------------------------|
| Sloan et al. [119]            | I                 | Hip fracture                | RCT          | Women aged >65 yr undergoing surgical fixation of hip fracture (N = 31) | Postoperative ND versus placebo | IM                      | 2 mg/kg administered weekly | 4 wk or until hospital discharge, whichever came first | 4 wk or until hospital discharge, whichever came first |
| Tidermark et al. [34]        | I                 | Hip fracture repair         | RCT          | Women aged >70 yr with BMI <24 kg/m² undergoing surgical fixation of femoral neck fracture, independent walking/living status (N = 60) | Postoperative ND + protein-rich formula + daily calcium and vitamin D versus protein-rich formula alone versus daily calcium and vitamin D alone | IM                      | 25 mg administered every 3 wk  | 6 mo                           | 12 mo                             |
| Hedstrom et al. [120]        | I                 | Hip fracture repair         | RCT          | Women aged >65 yr undergoing surgical fixation of hip fracture, independent living status (N = 63) | Postoperative ND + daily calcium and vitamin D versus daily calcium only | IM                      | 25 mg administered every 3 wk  | 12 mo                          | 12 mo                             |
| Hulsbæk et al. [124]         | I                 | Hip fracture repair         | RCT          | Adults aged >60 yr admitted to the hip fracture unit (n = 23) | Postoperative ND + protein-rich nutritional drinks vs placebo + protein-rich nutritional drinks | IM                      | Female: 50 mg; males: 100 mg or 200 mg dependent on total testosterone level every 3 wk | 14 wk                          | 14 wk                             |
| Wu et al. [32]               | I                 | ACL reconstruction          | RCT          | Otherwise healthy men aged 18-50 yr undergoing ACL reconstruction (N = 13) | Perioperative testosterone versus placebo, weekly IM testosterone 200 mg injections versus placebo. Injections began 2 wk before surgery to 6 wk postoperatively | IM                      | 200 mg administered weekly    | 8 wk, beginning 2 wk before surgery and continuing until 6 wk after surgery | 12 wk                             |

(continued)
exogenous testosterone use has never been studied in the context of improving ligament healing after injury, such as in the case of ACL reconstruction (Table 1). Still, the anabolic effects of AAS on muscle may improve postoperative recovery from knee injuries such as ACL tears. Knee injuries are associated with rapid disuse atrophy of the affected leg, which is worsened by surgical trauma and knee immobilization in the postoperative period.30,126 These factors contribute to a lengthy rehabilitative process but even with rehabilitation many patients do not return to preinjury activity levels.30,126

Preoperative rehabilitation mitigates loss of muscle mass and has been associated with a quicker return to sport.127 A recent clinical trial by Wu et al.35 evaluated whether testosterone supplementation would similarly minimize muscle loss in the leg after ACL reconstruction. Although the sample size (n = 13 males) precludes definitive conclusions, the authors found that testosterone-treated male patients had increased lean body mass relative to controls at 6 weeks post-ACL reconstruction.35 There were no differences in extensor muscle strength or clinical outcome scores between treatment groups, but the authors note that the study was underpowered to detect these differences.35 Additional studies are needed to determine the effect of perioperative testosterone on leg strength and outcomes after ACL reconstruction.

Total Joint Arthroplasty
Similar to the rationale described in the clinical scenarios above, short-term AAS use has also been studied in perioperative period of patients undergoing total joint arthroplasty (Table 1). An early study by Michelsen et al.128 reported that patients receiving large-dose nandrolone injection (200 mg) in the immediate postoperative period after total hip arthroplasty improved nitrogen balance and attenuated trauma-related myocyte amino acid changes. In a pilot clinical trial, Amory et al.129 investigated the effect of preoperative testosterone on inpatient functional recovery in patients undergoing total knee arthroplasty. Patients pretreated with four weeks of testosterone (600 mg intramuscularly, weekly) exhibited a trend toward shorter hospital stay and improvements in walking and stair climbing during inpatient rehabilitation.129

A pilot clinical trial published by Hohmann et al.36 in 2010 described 10 patients given nandrolone or a sham injection biweekly for 6 months after TKA. Despite the small sample size, the group treated with nandrolone exhibited greater quadriceps muscle strength at 3, 6, and 12 months postoperatively.36 In addition, patients from the AAS group performed better across all postoperative
Anabolic Steroids in Orthopaedic Surgery

functional testing, although only differences in the Knee Society Score at 6 weeks, 6 months, and 12 months reached statistical significance.\textsuperscript{36} Notably, the nandrolone group demonstrated decreased femoral and lumbar bone density, although these results were not statistically significant.\textsuperscript{36} As many patients undergoing TKA exhibit quadriceps deconditioning due to years of pain and inactivity, and the goal of TKA is to improve functional mobility, AAS may prove to be a useful adjunct in the perioperative period.

Summary

AASs have shown great promise as potential therapeutic tool in a variety of clinical scenarios relevant to orthopaedic surgeons. Based on current evidence, AASs can augment biological healing after muscle injury, fracture repair, or rotator cuff repair and have the potential to improve postoperative recovery after ACL reconstruction or total joint arthroplasty. To realize the clinical potential of AASs in orthopaedic surgery, substantial efforts are needed in the preclinical and clinical arenas to better characterize their effects on tissues and establish optimized regimens.

References

1. Haupt HA, Rovere GD: Anabolic steroids: A review of the literature. Am J Sports Med 1984;12:469-484.
2. Siperstein G, Romano N, Iskenderoglou G, Roman A, Fowler FJ Jr, Drascher M: The American Public’s Perception of Illegal Steroid Use: A National Survey. 2013, Boston, MA: University of Massachusetts, 2013.
3. McDuff D, Stull T, Castaldelli-Maia JM, Hitchcock ME, Hainline B, Reardon CL: Recreational and ergogenic substance use and substance use disorders in elite athletes: A narrative review. Br J Sports Med 2019;53:754-760.
4. Basaria S, Wahlstrom JT, Dobs AS: Anabolic-androgenic steroid therapy in the treatment of chronic diseases. J Clin Endocrinol Metab 2001;86:5108-5117.
5. Casaburi R, Nakata J, Bistrong L, Torres E, Rambod M, Porszasz J: Effect of megestrol acetate and testosterone on body composition and hormonal responses in COPD cachexia. Chronic Obstr Pulm Dis 2015;3:389-397.
6. Dudgeon WD, Phillips KD, Carson JA, Brewer RB, Durstine JL, Hand GA: Counteracting muscle wasting in HIV-infected individuals. HIV Med 2006;7:299-310.
7. Ferrando AA, Sheffield-Moore M, Wolf SE, Heird WN, Wolfe RR: Testosterone administration in severe burns ameliorates muscle catabolism. Crit Care Med 2001;29:1936-1942.
8. Li H, Guo Y, Yang Z, Roy M, Guo Q: The efficacy and safety of oxandrolone treatment for patients with severe burns: A systematic review and meta-analysis. Burns 2016;42:717-727.
9. Wright TJ, Dillon EL, Durham WJ, et al: A randomized trial of adjunct testosterone for cancer-related muscle loss in men and women. J Cachexia Sarcopenia Muscle 2018;9:482-496.

10. Wischmeyer PE, Suman OE, Kozar R, Wolf SE, Molinger J, Pastva AM: Role of anabolic testosterone agents and structured exercise to promote recovery in ICU survivors. Curr Opin Crit Care 2020;26:508-515.
11. Giangregorio L, McCartney N: Bone loss and muscle atrophy in spinal cord injury: Epidemiology, fracture prediction, and rehabilitation strategies. J Spinal Cord Med 2006;29:489-500.
12. Yarrow JF, Conover CF, Begg LA, et al: Testosterone dose dependently prevents bone and muscle loss in rodents after spinal cord injury. J Neurotrauma 2014;31:834-845.
13. Gorgey AS, Khalil RE, Gill R, et al: Effects of testosterone and evoked resistance exercise after spinal cord injury (TEREX-SCI): Study protocol for a randomised controlled trial. BMJ open 2017;7:e014125.

14. Bagattel CJ, Bremner WJ: Androgens in men—Uses and abuses. N Engl J Med 1996;334:707-714.
15. Bhagin S, Woodhouse L, Casaburi R, et al: Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001;281:E1172-E1181.
16. Kuhn CM: Anabolic steroids. Recent Prog Horm Res 2002;57:411-434.
17. Sinha-Hikim I, Artaza J, Woodhouse L, et al: Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. Am J Physiol Endocrinol Metab 2002;283:E154-E164.
18. Labrie F: Methods for preventing and treating osteoporosis with low dose non-masculinizing androgenic compounds. Google Patents, 1996.
19. Anderson F, Francis R, Peaston R, Wastell H: Androgen supplementation in eugonadal men with osteoporosis: Effects of six months’ treatment on markers of bone formation and resorption. J Bone Mineral Res 1997;12:472-478.
20. Geusens P: Nandrolone decanoate: Pharmacological properties and therapeutic use in osteoporosis. Clin Rheumatol 1995;14:32-39.
21. Kirby DJ, Buchalter DB, Anil U, Leucht P: DHEA in bone: The role in osteoporosis and fracture healing. Arch Osteoporos 2020;15:84.
22. Huang K, Cai HL, Bao JP, Wu LD: Dehydroepiandrosterone and age-related musculoskeletal diseases: Connections and therapeutic implications. Ageing Res Rev 2020;62:101132.
23. Watts NB, Adler RA, Bilezikian JP, et al: Osteoporosis in men: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:1802-1822.
24. Frisoli A Jr, Chaves PH, Pinheiro MM, Szejnfeld VL: The effect of nandrolone decanoate on bone mineral density, muscle mass, and hemoglobin levels in elderly women with osteoporosis: A double-blind, randomized, placebo-controlled clinical trial. J Gerontol A Biol Sci Med Sci 2005;60:648-653.
25. Need AG, Durbridge TC, Nordin BE: Anabolic steroids in postmenopausal osteoporosis. Wien Med Wochenschr 1993;143:392-396.
26. Need AG, Horowitz M, Bridges A, Morris HA, Nordin BCC: Effects of nandrolone decanoate and anti-resorptive therapy on vertebral density in osteoporotic postmenopausal women. Arch Intern Med 1989;149:57-60.
27. Passeri M, Pedrazzoni M, Pioi G, Buttolini L, Ruys AH, Cortenraad MG: Effects of nandrolone decanoate on bone mass in established osteoporosis. Maturitas 1993;17:211-219.
28. Evans NA: Current concepts in anabolic-androgenic steroids. Am J Sports Med 2004;32:534-542.
29. Manimuthu K, Murton AJ, Greenhafl PL: Mechanisms regulating muscle mass during disuse atrophy and rehabilitation in humans. J Appl Physiol (1985) 2011;110:555-560.
alpha-reductive steroid metabolism in the dissociation of “myotropic” and “androgenic” activities of 19-nortestosterone. J Steroid Biochem 1982;17: 653-660.
50. Yu JG, Bonnurup P, Eriksson A, Stål PS, Tegner Y, Malm C: Effects of long term supplementation of anabolic androgen steroids on human skeletal muscle. PLoS One 2014;9:e105330.
51. Almeida M, Laurent MR, Duboix V, et al: Estrogens and androgens in skeletal physiology and pathophysiology. Physiol Rev 2017;97:153-187.
52. Guzzoni V, Selistre-de-Araujo HS, Marqueti RC: Tendon remodeling in response to resistance training, anabolic androgenic steroids and aging. Cells 2018;7:251.
53. Hamlet WP, Liu SH, Panossian V, Finerman GA: Primary immunolocalization of androgen target cells in the human anterior cruciate ligament. J Orthop Res 1997;15:657-663.
54. Sinha-Hikim I, Taylor WE, Gonzalez-Cadavid NF, Zheng W, Bhasin S: Androgen receptor in human skeletal muscle and cultured muscle satellite cells: Up-regulation by androgen treatment. J Clin Endocrinol Metab 2004; 89:5245-5255.
55. Duboix V, Laurent M, Boonen S, Vanderschueren D, Claessens F: Androgens and skeletal muscle: Cellular and molecular action mechanisms underlying the anabolic actions. Cell Mol Life Sci 2012;69:1651-1667.
56. MacLean HE, Chiu WS, Notini AJ, et al: Impaired skeletal muscle development and function in male, but not female, gonadoregulated receptor knockout mice. FASEB J 2008;22:2676-2689.
57. Nieł L, Shah AH, Lewis GA, et al: Sexual differentiation of the spinal nucleus of the bulbocavernosus is not mediated solely by androgen receptors in muscle fibers. Endocrinology 2009;150:3207-3213.
58. Ophoff J, Van Proeyen K, Callewaert F, et al: Androgen signaling in myocytes contributes to the maintenance of muscle mass and fiber type regulation but not to muscle strength or fatigue. Endocrinology 2009:150:3558-3566.
59. Brodsky IG, Balagopapal N, Nair KS: Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men—A clinical research center study. J Clin Endocrinol Metab 1996;81: 3469-3475.
60. Schroeder ET, Terk M, Sattler FR: Androgen therapy improves muscle mass and strength but not muscle quality: Results from two studies. Am J Physiol Endocrinol Metab 2003;285:E16-E24.
61. Manolagas SC, O’Brien CA, Almeida M: The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol 2013; 9:699-712.
62. Kawano H, Sato T, Yamada T, et al: Suppressive function of androgen receptor in bone resorption. Proc Natl Acad Sci U S A 2003;100: 9416-9421.
63. Callewaert F, Venken K, Ophoff J, et al: Differential regulation of bone and body composition in male mice with combined inactivation of androgen and estrogen receptor-alpha. FASEB J 2009;23:232-240.
64. Ucer S, Iyer S, Bartell SM, et al: The effects of androgens on murine cortical bone do not require AR or ERα signaling in osteoblasts and osteoclasts. J Bone Miner Res 2013;30:1138-1149.
65. Behra HM, Klesch S, Leifke E, Link TM, Nieschlag E: Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82:2386-2390.
66. Walsh JS, Eastell R: Osteoporosis in men. Nat Rev Endocrinol 2013;9: 637-645.
67. Rairy CM, Ratcliffe SJ, Weinstein R, et al: Higher serum free testosterone concentration in older women is associated with greater bone mineral density, lean body mass, and total fat mass: The cardiovascular health study. J Clin Endocrinol Metab 2011;96:989-996.

30. Arangio GA, Chen C, Kalady M, Reed JF: III: Thigh muscle size and strength after anterior cruciate ligament reconstruction and rehabilitation. J Orthop Sports Ther 1997;26:238-243.
31. Mizner RL, Pettersson SC, Snyder-Mackler L: Quadriceps strength and the time course of functional recovery after total knee arthroplasty. J Orthop Sports Phys Ther 2003;35:424-436.
32. Mizner RL, Pettersson SC, Stevens JE, Vandenbome K, Snyder-Mackler L: Early quadriceps strength loss after total knee arthroplasty. The contributions of muscle atrophy and failure of voluntary muscle activation. J Bone Joint Surg Am 2005;87:1047-1053.
33. Siu AL, Penrod JD, Boocock K, Koval K, Strauss E, Morrison RS: Early ambulation after hip fracture: Effects on function and mortality. Arch Intern Med 2006;166:766-771.
34. Tarantino U, Baldi J, Scimeca M, et al: The role of sarcopenia with and without fracture. Injury 2016;47(suppl 4):S3-S10.
35. Wu B, Lorenzana D, Badash I, et al: Perioperative testosterone supplementation increases lean mass in healthy men undergoing anterior cruciate ligament reconstruction: A randomized controlled trial. Orthop J Sports Med 2017;5:2325967117722794.
36. Hohmann E, Tetsworth K, Hohmann S, Bryant AL: Anabolic steroids after total knee arthroplasty. A double blinded prospective pilot study. J Orthop Surg Res 2010;5:93.
37. Tidemark J, Porzner S, Carlsson P, et al: Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. Clin Nutr 2004;23:587-596.
38. Tarsoly E, Jánossy J, Kosztura L: Effect of testosterone on fracture healing in hypophysectomized rats. Acta Histochem 1979;65:25-33.
39. Gerber C, Meyer DC, Fluck M, Benn MC, von Rechenberg B, Wieser K: Anabolic steroids reduce muscle degeneration associated with rotator cuff tendon release in sheep. Am J Sports Med 2016;44:2393-2400.
40. Gerber C, Meyer DC, Nuss KM, Farshad M: Anabolic steroids reduce muscle damage caused by rotator cuff tendon release in an experimental study in rabbits. J Bone Joint Surg Am 2011;93:2189-2195.
41. Gerber C, Meyer DC, Von Rechenberg B, Hoppeler H, Frigg R, Farshad M: Rotator cuff muscles lose responsiveness to anabolic steroids after tendon tear and muscularocutaneous retraction: An experimental study in sheep. Am J Sports Med 2012;40:2454-2461.
42. Ensor KL, Kwon YW, Dibeneditto MR, Zuckerman JD, Rokito AS: The rising incidence of rotator cuff repairs. J Shoulder Elbow Surg 2013;22: 1628-1632.
43. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teeffy SA: The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am 2006;88:1699-1704.
44. Carson JA, Manolagas SC: Effects of sex steroids on bones and muscles: Similarities, parallels, and putative interactions in health and disease. Bone 2015;80:67-78.
45. Celotti F, Negri Cesì P: Anabolic steroids: A review of their effects on the muscles, of their possible mechanisms of action and of their use in athletics. J Steroid Biochem Mol Biol 1992;43:469-477.
46. Kicman AT: Pharmacology of anabolic steroids. Br J Pharmacol 2008; 154:502-521.
47. Davey RA, Grossmann M: Androgen receptor structure, function and biology: From bench to bedside. Clin Biochem Rev 2016;37:3-15.
48. Mayer M, Rosen F: Interaction of anabolic steroids with glucocorticoid receptor sites in rat muscle cytosol. Am J Physiol 1975;229:1381-1386.
49. Töth M, Zakár T: Relative binding affinities of testosterone, 19-nortestosterone and their 5 alpha-reduced derivatives to the androgen receptor and to other androgen-binding proteins: A suggested role of 5 alpha-reductive steroid metabolism in the dissociation of “myotropic” and “androgenic” activities of 19-nortestosterone. J Steroid Biochem 1982;17: 653-660.
68. Kanayama G, DeLuca J, Meehan WP III, et al: Ruptured tendons in anabolic-androgenic steroid users: A cross-sectional cohort study. Am J Sports Med 2015;43:2638-2644.

69. Jones IA, Togashi R, Hatch GFR III, Weber AE, Vangsness CT Jr: Anabolic steroids and tendons: A review of their mechanical, structural, and biologic effects. J Orthop Res 2018;36:2830-2841.

70. Marquetti RC, Heinemeier KM, Durigan JL, et al: Gene expression in distinct regions of rat tendons in response to jump training combined with anabolic androgenic steroid administration. Eur J Appl Physiol 2012;112:1505-1515.

71. Karpakka JA, Pesola MK, Takala TE: The effects of anabolic steroids on collagen synthesis in rat skeletal muscle and tendon. A preliminary report. Am J Sports Med 1992;20:262-266.

72. Lovering RM, Romani WA: Effect of testosterone on the female anterior cruciate ligament. Am J Physiol Regul Integr Physiol 2005;289:R15-R22.

73. Romani WA, Belkoff SM, Elisseeff JH: Testosterone may increase rat anterior cruciate ligament strength. Knee 2016;23:1069-1073.

74. Tipton CM, Tcheng TK, Mergner W: Ligamentous strength measurements from hypophysectomized rats. Am J Physiol 1971;212:1144-1150.

75. Yu WD, Liu SH, Hatch JD, Panossian V, Finerman GA: Effect of estrogen on collagen synthesis in rat skeletal muscle and tendon. A preliminary report. Am J Physiol Regul Integr Physiol 2001:268-281.

77. Griffin LY, Agej J, Albohm MJ, et al: Noncontact anterior cruciate ligament injuries: Risk factors and prevention strategies. J Am Acad Orthop Surg 2000;8:141-150.

78. Hoffman JR, Ratamess NA: Medical issues associated with anabolic steroid use: Are they exaggerated? J Sports Sci Med 2006;6:182-193.

79. Evans NA: Gym and tonic: A profile of 100 male steroid users. J Sports Sci Med 2006;5:182-193.

80. Hartgens F, Kuipers H: Effects of androgenic-anabolic steroids in the elderly. J Clin Endocrinol Metab 1996;73:1252-1262.

82. Clark AS, Henderson LP: Behavioral and physiological responses to anabolic/androgenic steroids and physical exercise on isometric contractile properties of regenerating skeletal muscles in the rat. Arch Physiol Biochem 2000;108:257-261.

83. Strauss RH, Liggett MT, Lanese RR: Anabolic steroid use and perceived effects in ten weight-trained women athletes. J Clin Endocrinol Metab 1997;82:407-413.

84. Bhasin S, Storer TW, Berman N, et al: Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 1999;84:413-436.

85. Strauss RH, Liggett MT, Lanese RR: Anabolic steroid use and perceived effects in ten weight-trained women athletes. JAMA 1985;253:2871-2873.

86. Bhasin S, Storer TW, Berman N, et al: Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 1997;82:407-413.

87. Schroeder ET, Singh A, Bhasin S, et al: Effects of an oral androgen on muscle and metabolism in older, community-dwelling men. Am J Physiol Endocrinol Metab 2003;284:E120-E128.

88. Auyeung TW, Lee JS, Krook T, et al: Testosterone but not estradiol level is positively related to muscle strength and physical performance independent of muscle mass: A cross-sectional study in 1489 older men. Eur J Endocrinol 2011;164:811-817.

89. Beiner JM, Joly P: Muscle atrophy in anabolic steroids. J Am Acad Orthop Surg 2000;8:122-237.

90. Chargé SB, Rudnicki MA: Cell death and anabolic-androgenic steroid therapy. Physiol Rev 2004;84:200-238.

91. Noonan T, Garrett WE Jr: Muscle repair: In vivo studies. J Am Acad Orthop Surg 1999;7:262-269.

92. Jackson DW, Feagin JA: Quadriceps contusions in young athletes. J Am Acad Orthop Surg 1993;11:229-237.

93. Lynch GS, Schertzer JD, Ryall JD: Anabolic agents for improving muscle regeneration and function after injury. J Bone Joint Surg Am 1973;55:95-105.

94. Ferré A, Núñez P, Page CL, Sáenz IB, Daegelen D, Rieu M: Effects of anabolic/androgenic steroids on regenerating skeletal muscles in the rat. Acta Physiol Scand 1999;166:105-110.

95. Ferré A, Vignaud A, Núñez P, Bertucci W: Effects of anabolic/androgenic steroids and physical activity on the contractile properties of regenerating skeletal muscles in the rat. Arch Physiol Biochem 2010;108:257-261.

96. Beiner JM, Joly P, Cholewicki J, Panjabi MM: The effect of anabolic steroids and corticosteroids on muscle strength and function in older men. J Orthop Sports Phys Ther 1999;29:101-108.

97. White JP, Baltgavisa KA, Sato S, Wilson LB, Carson JA: Effect of nandrolone decanoate administration on recovery from bupivacaine-induced muscle injury. J Appl Physiol 2009;107:1420-1430.

98. Serra C, Tangerlini F, Rudy S, et al: Testosterone improves the regeneration of old and young mouse skeletal muscle. J Gerontol A Biol Sci Med Sci 2013;68:17-26.

99. Einhorn TA, Gerstenfeld LC: Fracture healing: Mechanisms and interventions. Nat Rev Rheumatol 2015;11:45-54.

100. Franklin M, Borrelli J: The effects of testosterone propionate and methandrostenolone enanthate on the healing of humeral osteotomies in the Wistar rat. J Invest Surg 1990:93-113.

101. Benghuzzi H, Tucci M, Tsao A, Russell G, England B, Ragab A: Stimulation of osteogenesis by means of sustained delivery of natural androgenic hormones. Bone 2004;40:99-104.

102. Gordon E, Lasserre A, Stull P, Bajpai PK, England B: A zinc based self setting ceramic bone substitute for local delivery of testosterone. Bone 2004;33:131-136.

103. Zafirou W, Parker D, Billotte W, Bajpai PK: Development of a ceramic device for the continuous local delivery of steroids. Biomed Sci Instrum 1996;32:63-70.

104. Cheng BH, Chu TM, Chang C, Kag HY, Huang KE: Testosterone delivered with a scaffold is as effective as bone morphologic protein-2 in promoting the repair of critical-size segmental defect of femoral bone in mice. PLoS One 2013;8:e70234.

105. Epstein NE: Pros, cons, and costs of INFUSE in spinal surgery. Surg Neurol Int 2011;2:10.

106. Boileau P, Brassart N, Watkinson DJ, Carles M, Hatzidakis AM, Krishnan SG: Arthroscopic repair of full-thickness tears of the rotator cuff. Am J Sports Med 2016;44:231-240.

107. Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K: The outcome and repair integrity of completely arthroscopically repaired tears of the rotator cuff. J Bone Joint Surg Am 2000;82:505-515.

108. Gerber C, Fuchs B, Hodler J: The results of repair of massive tears of the rotator cuff. J Bone Joint Surg Am 2000;82:505-515.

109. Gerber C, Meyer DC, Schneeberger AG, Hoppeler H, von Rechenberg B: Effect of tendon release and delayed repair on the structure
of the muscles of the rotator cuff: An experimental study in sheep. J Bone Joint Surg Am 2004;86:1973-1982.

110. Goutallier D, Postel JM, Bernageau J, Lavau L, Voisin MC: Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin Orthop Relat Res 1994;304:78-83.

111. Thomsenau H, Rolland Y, Lucas C, Duval JM, Langlais F: Atrophy of the supraspinatus belly. Assessment by MRI in 55 patients with rotator cuff pathology. Acta Orthop Scand 1996;67:264-268.

112. Gladstone JN, Bishop JY, Lo IK, Flatow EL: Fatty infiltration and atrophy of the rotator cuff do not improve after rotator cuff repair and correlate with poor functional outcome. Am J Sports Med 2007;35:719-728.

113. Triantafillopolous IL, Banes AJ, Bowman KF Jr, Maloney M, Garrett WE Jr, Karas SG: Nandrolone decanoate and load increase remodeling and strength in human supraspinatus bioartificial tendons. Am J Sports Med 2004;32:934-943.

114. Marqueti RC, Parizotto NA, Chriguer RS, Perez SE, Selistre-de-Araujo HS: Androgenic-anabolic steroids associated with mechanical loading inhibit matrix metalloproteinase activity and affect the remodeling of the achilles tendon in rats. Am J Sports Med 2006;34:1274-1280.

115. Marqueti RC, Prestes J, Paschoal M, et al: Matrix metalloproteinase 2 activity in tendon regions: Effects of mechanical loading exercise associated to anabolic-androgenic steroids. Eur J Appl Physiol 2008;104:1087-1093.

116. Denaro V, Ruzzini L, Longo UG, et al: Effect of dihydrotestosterone on cultured human tenocytes from intact supraspinatus tendon. Knee Surg Sports Traumatol Arthrosc 2010;18:971-976.

117. Papaspiropoulos A, Papapaskeva K, Papadopoulou E, Ferroussis J, Papalois A, Zoubos A: The effect of local use of nandrolone decanoate on rotator cuff repair in rabbits. J Invest Surg 2010;23:204-207.

118. Clinica/Trials.gov. Oxandrolone Rotator Cuff Trial (ORCT). Los Angeles, CA: University of Southern California. 2017.

119. Bhandari M, Swiontkowski M: Management of acute hip fracture. N Engl J Med 2017;377:2053-2062.

120. Dennison E, Mohamed MA, Cooper C: Epidemiology of osteoporosis. Rheum Dis Clin North Am 2006;32:617-629.

121. Farooqi V, van den Berg MEL, Cameron ID, Croft M: Anabolic steroids for rehabilitation after hip fracture in older people. Cochrane Database Syst Rev 2014;2014:CD008887.

122. Sloan JP, Wing P, Dian L, Meneilly GS: A pilot study of anabolic steroids in elderly patients with hip fractures. J Am Geriatr Soc 1992;40:1106–1111.

123. Hedstrom M, Sjoberg K, Brosjo E, Astrom K, Sjoberg H, Dalen N: Positive effects of anabolic steroids, vitamin D and calcium on muscle mass, bone mineral density and clinical function after a hip fracture. A randomised study of 63 women. J Bone Joint Surg Br 2002;84:497-503.

124. Hulsbæk S, Bandholm T, Ban I, et al: Feasibility and preliminary effect of anabolic steroids in addition to strength training and nutritional supplement in rehabilitation of patients with hip fracture: A randomized controlled pilot trial (HIP-SAP1 trial). BMC Geriatr 2021;21:323.

125. Tengstrand B, Cederholm T, Soderqvist A, Tidermark J: Effects of protein-rich supplementation and nandrolone on bone tissue after a hip fracture. Clin Nutr 2007;26:460-465.

126. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS: A randomized trial of treatment for acute anterior cruciate ligament tears. N Engl J Med 2010;363:331-342.

127. Shaarani SR, O’Hare C, Quinn A, Mcyna N, Moran R, O’Byrne JM: Effect of prehabilitation on the outcome of anterior cruciate ligament tears. N Engl J Med 2010;363:331-342.

128. Michelsen CB, Askanazi J, Kinney JM, Gump FE, Elwyn DH: Effect of an anabolic steroid on nitrogen balance and amino acid patterns after total hip replacement. J Trauma 1982;21:410-413.

129. Amory JK, Chansky HA, Chansky KL, et al: Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. J Am Geriatr Soc 2002;50:1698-1701.