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Anabolic steroid-induced hypogonadism – Towards a unified hypothesis of anabolic steroid action

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SUMMARY

Anabolic steroid-induced hypogonadism (ASIH) is the functional incompetence of the testes with subnormal or impaired production of testosterone and/or spermatozoa due to administration of androgens or anabolic steroids. Anabolic–androgenic steroid (AAS), both prescription and nonprescription, use is a cause of ASIH. Current AAS use includes prescribing for wasting associated conditions. Nonprescription AAS use is also believed to lead to AAS dependency or addiction. Together these two uses account for more than four million males taking AAS in one form or another for a limited duration. While both of these uses deal with the effects of AAS administration they do not account for the period after AAS cessation. The signs and symptoms of ASIH directly impact the observation of an increase in muscle mass and muscle strength from AAS administration and also reflect what is believed to demonstrate AAS dependency. More significantly, AAS prescribing after cessation adds the comorbid condition of hypogonadism to their already existing chronic illness. ASIH is critical towards any future planned use of AAS or similar compound to effect positive changes in muscle mass and muscle strength as well as an understanding for what has been termed anabolic steroid dependency. The further understanding and treatments that mitigate or prevent ASIH could contribute to androgen therapies for wasting associated diseases and stopping nonprescription AAS use. This paper proposes a unified hypothesis that the net effects for anabolic steroid administration must necessarily include the period after their cessation or ASIH.

Introduction

The development of AAS compounds was originally for treatment of hypogonadal dysfunction and commencement of delayed puberty in men and for growth promotion [1]. AAS have, however, not always been used for pure medical purposes. Due to their anabolic effects, AAS became vastly popular among athletes, bodybuilders, and power lifters. Moreover, scientific and official court documents, including doctoral theses and scientific reports, demonstrate the positive effects of these and other hormonal drugs on muscle strength and performance in elite sports, which was common knowledge and had been in practice since the early 1960s [2].

Controversy raged for decades over the effectiveness of AAS in promoting muscle mass and muscle strength. Despite the admitted illicit use of AAS by athletes, the record breaking in Olympic events, and the obvious appearance in musculature enhancement, the medical and research community disputed and denied the AAS effects [3,4]. After a considerable period of scientific controversy, it is now clear that anabolic–androgenic steroid hormones are effective in increasing both muscle mass and muscle strength [5].

Another of the beliefs held by the medical community deals with the period after anabolic steroid cessation, not their administration. The prevailing medical opinion is that clinically significant ASIH occurs from nonprescription AAS use but not from clinically prescribed AAS [6,7]. The signs and symptoms of ASIH will necessarily impact upon our understanding for the clinical use of AAS. Additionally, these very same signs and symptoms might be instrumental in what has been described as AAS dependency.

Anabolic steroid-induced hypogonadism (ASIH)

Anabolic–androgenic steroids (AAS) are a class of compounds that include any drug or hormonal substance, chemically and pharmacologically related to testosterone that stimulates the growth or manufacturing of bone and muscle. It has long been held that nonprescription AAS use results in a functional type of hypogonadotropic hypogonadism. Boje was the first physician to suggest, in 1939, that AAS might enhance athletic performance, but he was also the first to forewarn athletes of potential health effects of steroids.

For over a quarter century, publications demonstrate HPTA suppression after nonprescription anabolic steroid use. Consistently, there is found a dramatic suppression of serum gonadotropins and testosterone levels that continues for an indefinite period after

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AAS cessation [8–10]. In 2003, a retrospective study examined the effects of illicit AAS on a population in which the mean time off steroids was 43 months with the minimum length of time 1 year and the maximum 10 years. The study found 13/15 ex-AAS users were in the lower 20 percent of the normal reference range for testosterone and 2/15 were below the normal range [11]. Another well-described event are reports citing long periods for the return of spermatogenesis after nonprescription AAS use, include continuing azoospermia [6,12,13]. Contrary to the belief that nonprescription AAS doses are 10–100-fold greater than those clinically prescribed, reports include doses approximately twice that for replacement therapy [10].

Similarly, during the same timeframe documentation in peer-reviewed literature shows AAS prescribing with clinical doses and durations to cause both gonadotropin suppression and decreased serum testosterone after AAS cessation [14–16]. The authors went so far as to warn that anabolic steroid administration is a possible cause for hypogonadism [15]. Birth control studies with testosterone administration in physiological as well as sub-physiological doses demonstrate HPTA suppression and continuing infertility [17,18]. More recent studies and reviews on androgen and androgen/progestin male contraceptives confirm the offset of reliable contraception and of resumption of normal male fertility to baseline values can be up to 2 years [19,20]. Finally, even the FDA approved labeling PDR for AAS contain the adverse effects of HPTA suppression, inhibition of testicular function, testicular atrophy, oligospermia, impotence, and more.

Published literature uniformly finds AAS administration, both prescription and nonprescription, induces a state of hypogonadism after AAS cessation. All compounds classified as anabolic–androgenic steroids cause a negative feedback inhibition of the hypothalamic pituitary testicular axis, suppress endogenous gonadotropin secretion, and as a consequence endogenous testosterone production. After AAS administration, HPTA suppression follows, with the variables being the duration and severity.

ASIH, as a form of hypogonadism, is a real disease with potentially serious consequences. Declining, or suppressed, circulating testosterone levels because of either pathophysiological or induced hypogonadal conditions can have many negative consequences in males. There is an association between hypogonadism (decreased levels of testosterone) and a number of signs and symptoms, most notably body composition changes (decrease in muscle mass and increase in fat mass), decreased muscle strength, bone loss, increased cardiovascular risk, sexual dysfunction (decreased libido, decreased spontaneous erections, decreased ejaculate, erection dysfunction, decreased sexual fantasies, and anorgasmia), decreased cognitive abilities (memory and concentration), sleep disturbances, adverse psychological effects (depression, low-self esteem, guilt, increased stress, and anhedonia), and constitutional symptoms (general fatigue, agitation/motor dyskinesia, and decreased appetite) [21]. These adverse effects have importance in an understanding for what has been called AAS dependency and the clinical use in wasting associated conditions of AAS for positive changes in muscle mass and muscle strength.

Psychological and behavioral effects

The association of AAS with adverse psychological and behavioral effects is extensive [22–32]. Historically, researchers went so far as to categorically state that AAS are without any evidence upon muscle going so far as to argue that there is saturation of the androgen receptor with eugonadal levels of testosterone. This attitude spurned the concept that the large doses commonly used by illicit AAS users indicate that the drug use is for actions other than their normal physiological effects, implying an addictive nature to AAS, with the signs and symptoms after AAS cessation indications of AAS withdrawal [33–37]. Upon nonprescription AAS cessation, psychological disturbances include aggressiveness, depression, anxiousness, potency problems (libido), sleep disorders, violent behavior, rage, and suicidal ideation [26,38,39].

The two most widely-accepted standards for defining, classifying and diagnosing drug abuse and dependence are the Diagnostic Statistical Manual IV (DSM-IV) and the International Classification of Diseases, Volume 10 (ICD-10). The Diagnostic Statistical Manual IV (DSM-IV) and the International Classification of Diseases, Volume 10 (ICD-10) differ in the way they regard anabolic–androgenic steroids' (AAS) potential for producing dependence [40]. DSM-IV regards AAS as potentially dependence producing and ICD 10 regards them as non-dependence producing.

This difference in approach towards AAS prompts debate as to whether or not AAS are dependence-producing substances. The main work in this area has been conducted by Brower et al. [34,36–38,41,42] who investigated the existence of a "steroid dependency syndrome" and classified subjects as dependent on AAS using an adaptation of the DSM-III-R [43] criteria for dependence on psychoactive substances, which differ only slightly from those of DSM-IV [44].

In 2002, Brower summarizes the literature on AAS abuse and dependence and reports of at least 165 cases of addiction or dependence in the medical literature [7]. Brower also concludes no cases of dependence have been associated with legitimate prescriptions of AAS used at therapeutic doses for medical purposes. According to Brower, individuals who use high doses of AAS over prolonged periods may develop withdrawal symptoms that include fatigue, depressed mood, restlessness, anhedonia, impaired concentration, increased aggression, anorexia, insomnia, decreased libido, self-image dissatisfaction, androgen desire, headaches, suicidal ideation, decrease in size/weight/strength, and feeling depressed/down/unhappy due to size loss when they stop taking AAS and these withdrawal effects may contribute to a syndrome of dependence. As the table shows below, the patient with hypogonadism may experience almost all of these above symptoms [21]. Rather than diagnosing substance abuse or dependence the criteria in use by these investigators for addiction is the patient examination for hypogonadism.

Symptoms of hypogonadism vs. dependence.

Dependence [34,36–38,41,42]	Hypogonadism [21]
Decrease in size/ weight/strength	Lean muscle loss
Impaired concentration	Decreased cognitive testing
Restlessness/ increased aggression	Agitation/motor dyskinesia
Depression/ depressed mood/ feeling depressed/ down/unhappy due to size loss	Depression
Suicidal ideation	Guilt
Self image dissatisfaction	Low-self esteem
Headaches	Increased stress
Fatigue	General fatigue
Insomnia	Sleep disturbances
Anorexia	Decreased appetite

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Decreased libido	Decreased libido
Anhedonia	Anhedonia
Withdrawal	Decreased spontaneous erections
Androgen desire	Decreased ejaculate
	Erection dysfunction
	Decreased sexual fantasies
	Anorgasmia

In 1990, the National Institute of Drug Abuse (NIDA) published an extensive monograph on anabolic steroid abuse [45]. This monograph represents a "state-of-the-art" information resource concerning anabolic steroid abuse. "It must be concluded at this time that the use of steroids by humans does not meet the criteria necessary to establish that steroids have significant abuse liability as defined in pharmacological terms". The conclusion from this monograph is anabolic steroids do not satisfy the criteria for abuse potential. Echoing this opinion is a report from President's Council on Physical Fitness. In 1994, evidence review of the published literature states, "Despite increasing clinical descriptive data on anabolic steroid withdrawal, dependence, and abuse, there are insufficient substantial basic or clinical research data to support the inclusion of these syndromes in DSM-IV" [46]. In the intervening 18 years since the original findings, there is nothing in the published scientific literature to change these conclusions. There are few, if any, well-controlled investigations or studies on the dependence potential of AAS.

In the future, studies on AAS dependency must include for the monitoring of hypogonadism. This paper proposes that these trials will support and affirm the hypothesis that the signs and symptoms previously attributed to dependency will be due to ASIH. Further, treatments aimed at preventing or mitigating ASIH will prove beneficial to stop AAS use.

Muscle effects

The idea that secretions of the testis might regulate body composition is as old as humanity itself. For decades, testosterone and testosterone analogues, anabolic–androgenic steroids (AAS), have long been used in the athletic community for improving muscle mass and muscle strength. Despite the obvious changes in musculature and appearance to even the most uninitiated, the academic community steadfastly refused to admit to any association. The scientific evidence shows the contrary to be true.

In 1996, Bhasin et al. reported testosterone administration causes an increase in muscle mass and muscle strength [5]. The investigation is not a clinical study for AAS treatment, but a study to separate out the effects of progressive resistance exercise and AAS on muscle mass and strength. Significantly, the research did not include the period after anabolic steroid administration. In spite of the known effects of AAS upon the HPTA, the evolution of AAS treatments for their ability to increase muscle mass and improve muscle strength began in earnest in the 1990s.

In many chronic illnesses, we can now achieve disease stability but not cure. In these chronic disorders, loss of muscle occurs frequently and is associated with debility, impaired quality of life, and poor disease outcome. Similarly, as men grow older, their muscle mass decreases and fat mass increases in association with a decline in testosterone levels. Therefore, strategies that can reverse muscle wasting and augment muscle function may reduce the burden of disease, improve quality of life, and reduce utilization of health care resources. Because of the effects of testosterone in enhancing lean body mass (LBM), muscle strength, and decreased adiposity studies investigate the possible role for testosterone or anabolic–androgenic steroids (AAS) in catabolic states. Anabolic–androgenic steroids have received particular attention with regard to improving body composition in those with chronic illness.

The current prescribing of AAS, including testosterone, is for sarcopenia (loss of muscle mass and muscle strength with ageing), chronic kidney disease (hemodialysis), HIV+ males, chronic obstructive pulmonary disease (COPD), osteoporosis, and long-term glucocorticoid treatment [47–52]. The anabolic steroid research concludes that anabolic steroid administration results increases in muscle mass and muscle strength. Based on these conclusions, the physician-investigators recommend their use as a possible means of decreasing morbidity and mortality. These studies are indicative of the developing trend in using aggressive pharmacological therapy with anabolic steroids to reverse declines in lean body mass and muscle strength. On close inspection of these investigations where there is measurement of sex hormones or documentation of side-effects there is the universal finding of HPTA suppression.

In all of the studies that include muscle mass and muscle strength measurements both during and after AAS administration, the positive effects of AAS during their administration disappear in the period after stopping AAS [17,53]. In 2004, after years of published studies reporting on the positive benefits of AAS administration but with no follow-up for the period of hypogonadism after AAS cessation a randomized controlled study reported on the body composition changes during administration and after a 12-week follow-up period after AAS cessation [54]. The study found that the positive body composition changes in lean body mass, muscle area, and strength produced by the androgen in the study had completely disappeared 12 weeks after AAS cessation. Rather than recognize anabolic–androgenic steroid-induced hypogonadism as the critical factor for the loss of muscle mass and strength, these investigators suggest, "However, the benefits were lost within 12 weeks after oxandrolone was discontinued, suggesting that prolonged androgen treatment would be needed to maintain these anabolic benefits".

Each of the aforementioned studies examined the effects of AAS during their administration. Upon discontinuation of AAS, these patients would develop anabolic steroid-induced hypogonadism (ASIH), which negates the positive body composition changes and potentially leave them in a state of health worse than when first prescribed AAS. These studies utilizing AAS therapy have not identified what should be done to restore normal endocrine status post-treatment. The most significant concern is that marginally healthy individuals placed on AAS for this goal may be placing themselves at an even greater morbidity and mortality risk upon AAS cessation.

Interestingly, nonsteroidal androgen or selective androgen receptor modulators (SARM) administration is currently in the research and investigational stages for the same purposes as anabolic steroids. These studies indicate that their clinical use will result in induced hypogonadism after cessation by their effects on gonadotropin levels [55]. This same opinion was voiced by investigators that, "Selectivity with regard to gonadotropin suppression represents a significant barrier to the clinical use of SARMs" [56].

This does not mean that the use of androgens to promote positive changes in muscle mass and muscle strength needs to be abandoned. The better approach is to develop combinatorial therapies of androgens for an improvement in muscle mass and muscle

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strength followed by a treatment to prevent or minimize ASIH, thereby sustaining those positive changes.

Future treatments

A treatment goal of HPTA restoration will have its basis in the regulation and control of testosterone production. The HPTA has two components, both spermatogenesis and testosterone production. In males, luteinizing hormone (LH) secretion by the pituitary positively stimulates testicular testosterone (T) production; follicle-stimulating hormone (FSH) stimulates testicular spermatozoa production. The pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates LH and FSH secretion. In general, absent FSH, there is no spermatozoa production; absent LH, there is no testosterone production. Regulation of the secretion of GnRH, FSH, and LH occurs partially by the negative feedback of testosterone and estradiol at the level of the hypothalamo-pituitary. Estradiol has a much larger, inhibitory effect than testosterone, being 200-fold more effective in suppressing LH secretion [57–61].

In the case of ASIH, where the individual suffers from functional hypogonadism and the belief for eventual return of function, treatment is directed at HPTA restoration. A medical quandary for physicians presented with hypogonadal patients secondary to AAS administration is there is currently no FDA approved drug to restore HPTA function. Standard treatment to this point has been testosterone replacement therapy (TRT), human chorionic gonadotropin (hCG), conservative therapy (“watchful waiting” or “do nothing”), or off-label prescribing of aromatase inhibitors or selective estrogen receptor modulators (SERM).

The primary drawback of testosterone replacement and hCG administration is that this therapy is infinite in nature. These treatments will remedy the signs and symptoms associated with hypogonadism, but do not alleviate the need for a life-long commitment to therapy. Further, administration serves to further HPTA suppression. Conservative therapy (“watchful waiting” or “do nothing”) is the probably worst case option as this does nothing to treat the patient with ASIH. Also, conservative therapy will have the undesirable result of the nonprescription AAS user to return to AAS use as a means to avoid ASIH signs and symptoms.

The aromatase inhibitors demonstrate the ability to cause an elevation of the gonadotropins and secondarily serum testosterone [62]. The administration of SERMs is a common treatment in attempts to restore the HPTA because they increase LH secretion from the pituitary that leads to increased local testosterone production [63–67].

Guay has used clomiphene citrate as therapy for erection dysfunction and secondary hypogonadism. Patients received clomiphene citrate 50 mg per day for 4 months in an attempt to raise their testosterone level [68]. Clomiphene has been reported in a case study to reverse andropause secondary to anabolic–androgenic steroid use [69]. The patient received clomiphene citrate 50 mg twice per day in an attempt to raise his testosterone level. The patient when followed up after two months had a relapse, tiredness and loss of libido, after discontinuing clomiphene citrate.

There are case study reports demonstrating the effectiveness of the combination of clomiphene and tamoxifen in HPTA restoration after stopping AAS administration [70–73]. Clomiphene is a mixture of the *trans* (enclomiphene) and *cis* (zuclomiphene) enantiomers, which have opposite effects upon the estradiol receptor [74]. Enclomiphene is an estradiol antagonist, while zuclomiphene is an estradiol agonist. The addition of tamoxifen to clomiphene might be expected to increase the overall antagonism of the estradiol receptor. Enclomiphene alone might be a good candidate to restore HPTA function.

Discussion – a unified hypothesis

There are reports of the use of anabolic steroids by athletes since the 1950s to increase muscle size and strength to improve performance. Anabolic steroids use became more prominent in the athletic world, but use by the lay public has also increased. Long confined to bodybuilding and professional sports, the use of AAS is nowadays a problem that involves a wider population. In 2006, a report demonstrates that AAS use is common among males over 18 years [75]. In the United States, prevalence estimates are between 4% and 12% among adolescent males [76]. Current estimates from 2000 indicate that there are as many as three million AAS users in the United States and that 2.7–2.9% of adults have taken AAS at least once in their lives [77,78]. According to surveys and media reports, the illegal use of these drugs to increase muscle size and strength is widespread [79].

Anabolic–androgenic steroids are now commonly a prescribed drug for chronic illnesses, with estimates in the millions [47–52,80]. AAS treatment for these conditions is towards disease-associated morbidity, decreased muscle mass and decreased muscle strength, not treatment for the underlying disease cause. The treatment for these conditions is of a limited duration. In addition, adverse effects necessitate and require the discontinuation of these drugs. While the anecdotal and research reports of AAS benefits are inarguable, there is the real problem for failure to consider the period after their cessation, anabolic steroid-induced hypogonadism (ASIH).

Clinical application of published study results is dependent upon sound research design. In these studies, the intervention, AAS, causes a change in the prognosis in the treatment group. This introduces bias, making the conclusions invalid. Biased research results open the door for harm to patients extending far beyond those subjects involved in the clinical trial. These results may lead to erroneous conclusions about the safety or the efficacy of drugs. Researchers working on the next generation of research, creating a domino effect of error, will also use them. Once disseminated in the market, end user physicians and patients will pay the price for bad science in dollars, poor outcomes, and adverse events [81].

Importantly, a “good question” can be approached by good or bad research techniques; bad research methods do not render the question valueless. Thus, the significance of a hypothesis can and should be assessed prior to and independent of the specific research methods. Reviewers should not dismiss a proposal that uses inadequate methods without first considering whether adjustments could make the proposal scientifically valid.

Without definitive studies demonstrating there is no clinical consequence to ASIH after both prescription and nonprescription use, the understanding of AAS actions will be incomplete. Any hypothesis on AAS in health and disease requires a thorough understanding for the action not only during administration but also after their cessation. This paper proposes that clinically significant anabolic steroid-induced hypogonadism (ASIH) ensues for both illicit and licit AAS use after AAS cessation with the severity and duration unknown.

Moreover, treatments that mitigate or prevent ASIH will be useful not only in the treatment for the adverse psychological effects after stopping AAS, but also when used in combination with androgens to aid in the maintenance or sustaining of anabolic improvements sought in disorders marked by wasting. Finally, ASIH treatments might prove beneficial in mitigation of future post male contraceptive infertility. These need to be followed up with well-controlled clinical trials.

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