Title

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Journal

Proceedings of UCLA Health, 27(1)

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Publication Date

2023-07-24

CLINICAL VIGNETTE

Performance Enhancing Drug Use with Consequential Thromboembolism, Rhabdomyolysis and Hypertrophic Cardiomyopathy

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Introduction

Androgenic anabolic steroids (AAS) are performance-enhancing drugs that increase physiologic levels of testosterone, which stimulates protein synthesis and expedites muscle growth, body mass, and strength.[1,2] In addition to the anabolic effects of AAS, androgenic effects exerted on both reproductive and non-reproductive target tissues by testosterone play a major role in development of secondary sexual characteristics.[3] As such, a number of side effects of AAS have been reported in case studies and small cohort studies, including hormonal disturbances, reduced fertility, gynecomastia, hypertension, and psychological changes,[1,3] as well as more severe side effects including cardiotoxic sequelae[4-9] and venous thromboembolism (VTE).[10-13]

The thrombogenic nature of androgen use has been previously suggested in the literature.[14-16] While little research has focused on platelet activity in athletes using AAS, some studies suggest that excess AAS generates a prothrombotic state characterized by elevated platelet count and reactivity, leading to increased platelet aggregation.[17] Given that AAS-induced cardiovascular effects occur in young and healthy individuals, cardiotoxic sequelae from AAS excess is thought to be induced by atherothrombotic rather than atherogenic or vasospastic pathology.[18]

Since the 1940s, AAS have been commonly used by elite athletes and bodybuilders, with current estimated lifetime prevalence of use in men around 6%.[1,2] In recent years, other supplements commonly used along with AAS, such as growth hormone (GH) and clomiphene, have also been theorized to have potentially deleterious cardiac side effects such as ventricular dysfunction[12,18] and pulmonary embolism and VTE.[18,19] While surreptitious use of GH is illegal in the United States, GH abuse among athletes ranges from 5% (in a study of male high school athletes)[18] to 12% in a study of male weightlifters aged 18-40 years old.[19] Up to 1 in 3 users of androgenic steroids are reported to develop dependence.[20] Given relatively high prevalence of performance-enhancing drug use such as AAS, GH, and clomiphene as well as subsequent dependence, continued education in diagnosis and management of adverse effects from these substances is needed for appropriate provision of care.

Patient Summary

A 24-year-old male body builder presented to the ED with chest pain and DOE. In preparation for a body-building contest, he was taking anabolic steroids (testosterone injections 3x weekly) as well as growth hormone, anastrozole, and clomiphene. He was also adhering to a ketogenic diet and taking various supplements including pre-workout, protein powders, and creatine.

After his body building competition he did not go to the gym for a week and was attempting to taper off his testosterone with post-cycle therapy and clomiphene. He developed worsening myalgias, pleuritic chest pain, and SOB. On admission, a 12-lead EKG showed sinus rhythm with non-specific ST-T changes. A lower extremity doppler ultrasound was obtained and he was found to have lower extremity peroneal DVT and rhabdomyolysis on lab workup. A CT angiogram of the chest was inconclusive due to technical issues. Treatment with rivaroxaban 15mg daily was initiated for treatment of DVT and pulmonary embolism. An echocardiogram revealed mild-moderate pulmonary valve regurgitation and mild-moderate LVH with increased left ventricular wall texture concerning for infiltrative disease. The patient could not tolerate the MRI machine due to his size and thus a cardiac MRI was only partially completed. A summary of the main events of the hospitalization are listed below.

Date	**Significant Events**
Admission Hospital Day 1	Patient admitted with **CK of 9948 U/L** and US duplex with acute deep vein thrombosis involving one of paired peroneal veins of left lower extremity. Initial BNP level **109 pg/mL**. LFTs were elevated with AST at 299 U/L and ALT 401 U/L. Negative troponin. Pt's testosterone levels 2x ULN. Inconclusive CTA. Patient given IV fluids and started on Xarelto 15mg daily.

Admission Hospital Day 2	V/Q scan with no evidence for PE but small area of mildly decreased perfusion in posterior lateral aspect of the left lung. CK decreased from prior to **4,822 U/L.**
Admission Hospital Day 3	CK decreased from prior to **3153 U/L.** Cardiac MRI with mild concentric left ventricular myocardial hypertrophy, though the study was prematurely terminated. Pt discharged on Xarelto 15mg BID with meals x 21 days, then 20mg daily for 3-6 months with hematology-oncology follow-up. Pt also started on lisinopril daily for HTN and CMY.

Discussion

Use of anabolic steroids for performance enhancement has been commonly associated with heart disease such as left ventricular hypertrophy,[8,9] systolic dysfunction,[7] and impaired ventricular strain.[5] Much of the existing literature linking AAS use to cardiovascular pathology is cross-sectional precluding causal associations.[5-7] Findings from a prospective observational cohort study in 2015 strongly suggested cardiotoxic effects from AAS, specifically left ventricular hypertrophy and subsequent impairment of both systolic and diastolic function.[4]

The relationship between AAS use and development of VTE has also been proposed, primarily through individual case studies.[10-13] Although the pathophysiology for the association remains unclear, one model theorizes that AAS affects clotting factors and platelets, increasing coagulopathy through impaired fibrin clot lysis.[11,12] There is also limited evidence describing a relationship between AAS use and rhabdomyolysis, with one case study describing a subject who develop rhabdomyolysis after abrupt increase in exercise with concurrent AAS use.[21] Another study reported localized rhabdomyolysis at the site of injection of AAS into the shoulder region.[22]

The potential association between AAS use and thrombogenic sequelae such as VTE is thought to be mediated by androgen excess that leads to increased endoperoxides and thromboxane generation in platelets.[17] Research also suggests that AAS may elevate blood pressure and impair vascular reactivity, leading to polycythemia-induced hyperviscosity syndrome.[23] Prolonged and/or high doses of exogenous AAS have been shown to increase low-density lipoprotein-LDL cholesterol and triglycerides (and decrease high-density lipoprotein HDL cholesterol) by increasing plasma homocysteine levels, enhancing endothelial inflammation, and decreasing NO synthesis.[24] Each of these physiologic changes has independently been linked to coagulation abnormalities,[25, 26] the pathophysiology of AAS effects on pulmonary and cardiovascular risk is likely multifactorial.

Growth hormone (GH) is another substance commonly used to enhance athletic performance, often in combination with AAS. GH is thought to improve physical function through anabolic and lipolytic properties. Physiologically, GH is secreted in a pulsatile fashion and is regulated by insulin-like growth factor 1 (IGF-1) to stimulate protein synthesis in the body.[27] In adults with GH deficiency, GH supplementation has been shown to have beneficial effects on bone density, exercise capacity, and body composition.[28] However, there is little research on beneficial or adverse effects of GH when taken as a supplement to increase athletic performance. Limited data suggest associations between GH supplementation and side effects such as arthralgias, glucose intolerance/diabetes, carpal tunnel syndrome, and ventricular dysfunction.[7,18]

Finally, clomiphene is a substance commonly reported to be used alongside AAS and GH for performance enhancement. Traditionally used to treat infertility in women,[19] clomiphene is a selective estrogen receptor modulator that increases endogenous estrogen levels in women and testosterone levels in men through increased gonadotropin release. However, clomiphene misuse for performance enhancement has been thought to be associated with cardiovascular complications such as tachycardia, pulmonary embolism, palpitations, and deep vein thrombosis.[18,19]

Timely diagnosis of AAS and other performance-enhancing drug use may be challenging given that patients may be reluctant to disclose their substance use behaviors. As such, a trusting and therapeutic patient-provider relationship may facilitate prompt diagnosis. Other clinical features that may aid in the diagnosis include rapid increase in muscle strength and muscle mass, gynecomastia, acne, and small testes. In women, irregular menstruation, hirsutism, or virilization may provide clinical indications of exogenous hormone use.[29] Other features that may indicate excess androgen use in athletes include recreational or professional competition in a sport or activity, changes in behavior such as depression or irritability, or lab findings of low serum luteinizing hormone (LH) and low sex hormone-binding globulin).[29]

Patients who report willingness to stop using AAS and other performance-enhancing drugs should be encouraged to do so. However, patients are likely to be hypogonadal for up to one year before recovering endogenous gonadotropin secretion and testicular function.[29] A recent study from the Netherlands found that left ventricular hypertrophy among participants correlated with AAS average weekly dose and, after cessation of AAS use, cardiac mass returned to baseline after a median recovery time of 8 months.[4] However, one 2018 case study described cardiac complications of systolic and diastolic cardiomyopathy as well as ventricular tachycardia in a 73-year-old former Olympic athlete who previously misused AAS for 20 years, suggesting that there may be a dose duration or threshold for which cardiac effects are irreversible.[30] In addition, the physiologic cardiac remodeling effects of AAS may also be associated with an

increased risk of life-threatening arrhythmias that should be considered in the timely diagnosis and management of abuse of AAS and other performance-enhancing drugs such as GH and clomiphene.[31]

Conclusion

We report a case of DVT, LV hypertrophic cardiomyopathy and concurrent rhabdomyolysis secondary to AAS, GH, and clomiphene use in a patient without any prior risk factors for coagulopathy or abrupt increase in physical activity. AAS and other performance-enhancing drug use have been associated with cardiopulmonary pathology such as left ventricular hypertrophy, pulmonary embolism, cardiomyopathy, and impairment of systolic and diastolic function. While some studies suggest that these cardiac effects are reversible upon cessation of use, at least one study documents cases in which prolonged AAS use was associated with irreversible cardiomyopathy. As such, care providers should have a high index of suspicion when clinical signs suggesting AAS use are present and embrace open and non-judgmental patient-provider interactions to facilitate prompt diagnosis. Cessation of AAS and other drug use is recommended for management.

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