Health effects of androgen abuse: a review of the HAARLEM study

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Purpose of review
Data on the health effects of androgen abuse are mainly derived from lower level evidence, such as case series and cross-sectional studies. In the last few years a relatively large and prospective cohort initiative, the HAARLEM (health risks of anabolic androgenic steroid use by male amateur athletes) study, made an important contribution to current knowledge.

Recent findings
The HAARLEM study showed that all androgen abusers experience positive and negative effects, such as an increase in strength and acne and gynecomastia, respectively. Effects are generally reversible and acute life-threatening toxicity is rare. There is a distinct but limited impact on liver and kidney function. Gonadal function is disrupted but resumes normally after abuse is discontinued in the majority of athletes. The negative impact of androgens on cardiovascular parameters, such as blood pressure, hematocrit and lipid metabolism, as well as cardiac structure and function, seems to be the mechanism for premature atherosclerosis and cardiomyopathy, respectively, in long-term users.

Summary
It is beyond dispute that androgen abuse is harmful and much of the short-term toxicity is well documented. To prevent the long-term health hazards, there should be ample focus on preventive measures, both primary and secondary, and effective harm reduction strategies should be developed.

Keywords
anabolic steroids, androgen abuse, bodybuilding, doping in sports

INTRODUCTION

Androgens abused by strength athletes, also referred to as anabolic androgenic steroids, have the purpose of increasing strength and enhancing performance. Although the initial landscape of androgen abusers was confined to elite and competitive athletes, a gradual shift towards a large population of amateur athletes and ordinary gym-goers emerged around the 1980s and onwards [1]. Results of a 2014 meta-analysis estimated the global lifetime prevalence rate for males and females at 6.4% and 1.6%, respectively [2]. Although androgen abuse negatively impacts health, there is no broad understanding of its adverse effects. This is mainly due to unfamiliarity of the topic among health professionals and ethical barriers for conducting scientific research. Current data in literature is therefore mainly derived from expert opinion, case series, retrospective and cross-sectional studies.

In the last 2–3 years several publications reported data from the HAARLEM study [3,4▪–6▪,7], which is an acronym for health risks of anabolic androgenic steroid use by male amateur athletes. This cohort study takes precedence over much of the existing literature in this field due to its prospective design and relatively large size. It is a unique project that took place at the outpatient anabolic androgenic steroids clinic of the Spaarne Gasthuis in Haarlem, the Netherlands, between 2015 and 2019. It meticulously analyzed the health impact of real world androgen abuse and has become the current benchmark. Data from these reports lay an important foundation for appropriate education of athletes who consider, or already

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KEY POINTS

- Until recently, most evidence on health effect of androgen abuse was based on expert opinion, case studies, retrospective analysis and cross-sectional studies.
- The HAARLEM study provided real world data on androgen abuse by prospectively analyzing a relatively large group of strength athletes before, during and after a cycle.
- Androgen abuse caused adverse effects in all users, disrupted gonadal function, and negatively impacted cardiovascular parameters and cardiac structure and function.
- All adverse effects are generally reversible but ongoing or repeated use may cause long-term hazards, most importantly premature atherosclerosis and cardiomyopathy.
- Future research should focus on methods of primary and secondary prevention of androgen abuse, in which harm reduction strategies could play a pivotal role.

abuse, androgens and pave the way for the development of preventive measures. The current review will elaborate on, summarize, and discuss the most important findings of the HAARLEM study.

DESCRIPTION OF STUDIES

Data of the HAARLEM study were published in five different publications (see Table 1). The first described the demographic characteristics of the 100 subjects included in the study and the specifics of the androgen cycles performed by the athletes [3]. It also included a report of the qualitative testing results of 272 samples of black market androgen products provided by the subjects. The other publications summarized health analysis during a one year follow-up period, in which at least one androgen cycle was performed. Measurements took place before, during and twice after the cycle. Health effects were divided into several categories: positive and negative adverse effects reported by the subjects, the results of kidney and liver biochemistry in blood, and the outcome of psychological questionnaires [4▪]; the disruption and recovery of endogenous testosterone production and spermatogenesis [5▪]; the change of cardiovascular parameters during androgen abuse, such as blood pressure, lipid metabolism and erythrocytosis [6▪]; and change of cardiac structure and function as evaluated with 3D echocardiography [7].

Table 1. Overview of publications from the HAARLEM study each with the main theme and respective subjects addressed in the paper.

Baseline characteristics [3]
• Sociodemographic characteristics of androgen abusers
• Reported reasons and motivations for androgen abuse
• Methods of androgen abuse and cycle characteristics
• Quality of black market androgen products used by subjects
Positive and negative adverse effects [4▪]
• Prevalence of self-reported (positive and negative) adverse effects
• Prevalence of acne en gynecomastia during physical examination
• Prevalence of kidney and liver toxicity measured with blood analysis
• Psychological effects of androgen abuse (e.g. quality of life, depression)
Disruption of testicular function [5▪]
• The effect of androgen abuse on spermatogenesis during the cycle
• Rate of recovery of serum testosterone and spermatogenesis after the cycle
• The influence of postcycle therapy on the recovery of testicular function
Cardiovascular effects [6▪]
• The effect of androgen abuse on blood pressure, lipid profile and hematocrit
• Associations between cycle characteristics and observed cardiovascular effects
• Difference of the impact of oral and injectable androgens on lipid metabolism
Cardiac structure and function [7]
• The effect of androgen abuse on cardiac structure and function
• The reversibility of cardiac effects after discontinuation of androgens
• Associations between the observed effects and cycle characteristics

HAARLEM, health risks of anabolic androgenic steroid use by male amateur athletes.

BASELINE CHARACTERISTICS

One hundred study subjects were recruited for the HAARLEM study by presenting its concept on national television, in regional newspapers, and online discussion forums. Subjects were male strength athletes of at least 18 years old and intended to start a cycle on short notice. They were usually fanatic sportsmen that dedicated much of their time to vigorous training, averaging over 6 h per week in the gym. At enrollment, twenty subjects were new abusers of androgens. During a one-year follow-up period, an extensive health analysis took place at the beginning and at the end of the cycle, as well as three months after the cycle and one year after enrollment. The purpose was to first assess the extent of health effects caused by androgen abuse between the baseline and the second visit, and to

analyze the reversibility of those effects in the last two visits after a withdrawal period.

The typical cycle performed during the HAARLEM study was 13 weeks in duration, contained four different androgen types, and had a median weekly dose of 901 mg androgen equivalents. Subjects with a prior experience in androgen abuse or who were taking part in bodybuilding competitions had a tendency to perform longer, heavier cycles. A subject spent an average of €400 to retrieve products from his dealer or the internet. The backbone of almost every cycle was an injectable testosterone ester. Apart from this commonality, every single subject followed a different regimen, where – presumed to be – complementary androgen types, mostly trenbolone, drostanolone and boldenone, were combined with other performance and image-enhancing drugs (PIEDs), such as growth hormone, clenbuterol or thyroid hormone. Ancillary drugs to aid in recovery of endogenous testosterone production postcycle were taken by 80 subjects. This practice, also known as postcycle therapy (PCT), generally encompassed a combination of two agents, mostly tamoxifen, clomiphene citrate and/or human chorionic gonadotropin (hCG) for a median duration of 4 weeks.

SERIOUS ADVERSE EVENTS

Four subjects experienced serious adverse events, namely heart failure, acute pancreatitis, exacerbation of ulcerative colitis, and suicidal ideation. The case with heart failure concerned an individual with a hereditary hypertrophic cardiomyopathy which had been hitherto unknown. In the other three athletes, the event was a relapse of a previously known condition that had been diagnosed before and outside the context of androgen abuse. Based on these events, together with the large number of case reports of serious health issues due to androgen abuse, it could be postulated that androgen abuse can unhinge a – previously undisclosed – chronic illness or condition. Serious adverse events which are directly and solely the result of the short-term toxicity of androgens are probably very rare.

POSITIVE AND NEGATIVE SIDE EFFECTS

From the HAARLEM study it became clear that, upon questioning subjects about positive and negative adverse effects, for most subjects the androgen cycle had an obviously favorable risk-to-benefit ratio, at least on the short-term. Positive effects occurred in every user, not only an increased muscle mass (95%) and strength (100%), but also an increase in energy (45%) and an improved concentration (29%). These effects contrasted with negative effects such as fluid retention (56%), painful injection sites (20%) and diaphoresis (17%). These effects were generally considered mild and transitory. Indeed, a 13% minority of subjects had to stop or alter the androgen cycle due to adverse effects. Furthermore, physical examination revealed acne (29%) and gynecomastia (19%) in a subset of participants, but was also generally mild. After the cycle, positive effects quickly disappeared, and many subjects experienced a 'steroid dip', mainly consisting of a decreased libido (59%), sometimes erectile dysfunction (14%). This combination of events forms an important motive for users to start a new cycle or to perform a 'bridge' or maintenance dose of androgens between cycles.

KIDNEY AND LIVER TOXICITY

Blood analysis showed a small and reversible change of creatinine concentrations and dipstick analysis demonstrated albuminuria to emerge or increase in 16% of the subjects. The former may be attributed to an increase in muscle mass, the increased creatine synthesis in muscle tissue, or concurrent creatine supplementation [8,9]. In particular, creatine ethyl ester can lead to marked increases in serum creatinine concentrations [10].

Blood analysis also revealed a change in liver biochemistry, with small increments in alanine (ALT) and aspartate transferase (AST), which may reflect minor hepatic injury but often represents the muscle damage from heavy workouts, evidenced by a strong rise in creatine kinase concentrations in most subjects. Although there have been incidental reports of serious kidney [11] and liver [12] damage, data from the HAARLEM study could not demonstrate that high doses of androgens lead to clinical signs of considerable nephro- and hepatotoxicity.

TESTICULAR DYSFUNCTION

During an androgen cycle use there was an apparent disruption of testicular function. The administration of supraphysiological doses of exogenous androgens led to complete suppression of the hypothalamic–pituitary–gonadal axis in virtually all subjects. In accordance with this, testicular volume declined and spermatogenesis decreased. At the end of the cycle, three-quarters of subjects had a total sperm count below 40 million, and one-quarter had azoospermia. Interestingly, a longer duration of androgen abuse was not associated with a higher degree of suppression of spermatogenesis.

Recovery of testicular function after cessation of androgen abuse was less straightforward. When

gonadal function before the start of a cycle was normal, the chance of normalization of testosterone concentration was 90% after three months of recovery and 100% at the end of follow-up. This observation was independent of cycle dose or duration. Contrarily, 37% of cohort subjects had signs of abnormal gonadal function at baseline, and their recovery rate was slower with 24% not having a normal total testosterone concentration at the end of follow-up. This group was composed of subjects with a higher cumulative past androgen exposure, positing previous androgen abuse as a risk factor for long-lasting disruption of testicular function.

Spermatogenesis recovered more slowly than endogenous testosterone production, which is no surprise as it takes about 90 days before spermatozoa appear in the ejaculate after spermatogenesis resumes. Time to recovery of spermatogenesis, defined as a return of the total sperm count to baseline levels, was calculated at 59 weeks. This is consistent with the 14 months estimated by a recent large cross-sectional study [13]. It is very common for androgen abusers to start a new cycle before this roughly 1-year term and thus before recovery of spermatogenesis is complete. It is presumable that repeated exposure to androgens extends the required recovery time and may eventually even cause permanent distortion of fertility. Although some strength athletes use hCG during or after a cycle to support spermatogenesis, it is unclear whether this is effective, as black market hCG may not be genuine and regimens used are usually short and low-dosed.

CARDIOVASCULAR EFFECTS

Another health domain in which androgens play havoc is the cardiovascular system. There was a modest increase in blood pressure (+7/+3 mmHg) and causing 41% of subjects to be hypertensive (>140/90 mmHg) during the cycle compared to 16% at baseline. There is a similar picture for erythrocytosis, where androgen abuse led to a hematocrit of higher than 50% in one third of subjects compared to 5% at baseline. Both effects unfavorably impact cardiovascular disease risk [14,15]. A recent retrospective study found polycythemia secondary to testosterone replacement therapy to be an independent risk factor for major adverse cardiovascular events and venous thromboembolic events [16]. Interestingly, there was no observed dose-dependent effect between androgens and blood pressure and hematocrit in the HAARLEM study. As was the case with basically all androgen-induced effects, the untoward changes rapidly reversed back to baseline after cessation of androgen abuse.

The effect of androgens on lipid metabolism was more intricate. On the one hand, there was a clear adverse effect on low-density lipoprotein (LDL) cholesterol and apolipoprotein B (ApoB), and high-density lipoprotein (HDL) cholesterol and ApoA1. Two-thirds of the subjects used oral androgens in addition to injectable compounds, and the effects were worse in this group. On the other hand, the lipid parameter lipoprotein (a) (Lp(a)), which is strongly associated with cardiovascular disease [17], showed a mean decrease of 50% at the end of the cycle. The observed change of Lp(a) was inversely correlated with cycle dose and duration. The main question remains whether the observed beneficial reduction of Lp(a) can counterbalance the unfavorable effects induced by the other lipid parameters. Current evidence suggests this is not likely to be the case, as androgen abuse is associated with premature atherosclerosis and coronary artery disease [18].

An important lesson learnt from the observations on cardiovascular parameters is probably that cardiovascular risk of androgen abuse will not so much be determined by the magnitude of the changes of these parameters, but predominantly by the duration of androgen abuse. In other words, the longer a strength athlete abuses androgens in his sporting career, the worse his risk profile for cardiovascular disease will become. Many strength athletes who abuse androgens do so for just a few cycles and their cumulative exposure is less than a year, so their cardiovascular risk may not be elevated by much. Particularly troubling, however, is the cardiovascular risk of those athletes who perform many cycles after another, use high maintenance testosterone doses in between cycles, and/or are addicted to androgens and therefore not able to quit.

CARDIAC STRUCTURE AND FUNCTION

A subset of 31 athletes partaking in the HAARLEM study was included for comprehensive 3D echocardiographic examination. The findings confirmed the cardiotoxic nature of androgen abuse and were in accordance with a recent large cross-sectional study [19]. The analysis showed a clear increase in left ventricular mass, also after adjustment for body surface area, due to an enlarged interventricular septum and posterior wall. In addition, left ventricular ejection fraction decreased by 5% and left ventricular stiffness increased as illustrated by a significantly lower E/A-ratio. There was a positive relationship between average weekly androgen dose during the cycle and left ventricular mass. Although all parameters returned to their baseline values during recovery after the cycle, it is appealing to speculate that prolonged androgen abuse for longer

periods of time than in this study, or without sufficient time for full recovery between cycles, might induce nonreversible adverse changes in cardiac structure and function. This might also, partly, explain the recent death the recent death of several renowned bodybuilders with a long-standing history of androgen abuse [20].

LONG-TERM HAZARDS

There is thus convincing and detailed recently published prospective data about the short-term hazards of androgen abuse. It is, however, much less certain what repeated androgen exposure conveys in the long run. Athletes who abuse androgens for several years very often do so unhindered and never run into serious medical trouble. Especially worrisome is the risk of cardiovascular disease that androgen abuse may bring along, which may emerge no sooner than decades after an athlete starts his abuse, but the exact contribution of androgen abuse to cardiovascular risk remains largely undetermined. Future research should bridge this knowledge gap by prospectively following groups of previous androgen abusers or performing very large cross-sectional studies. The proper conduction of such research is challenged by ethical principles, which limit the availability of subjects and their willingness to participate, especially in countries where doping regulations are very strict.

Despite uncertainty about the long-term, the potential for health damage by androgen abuse arguably forms a spectrum, ranging from negligible for one or a few short cycles, to large in case an athlete performs dozens of cycles or uses androgens nonstop for many years. Therefore every user should be assessed and judged – not prejudiced – individually, taking into account the history of androgen abuse and probability of ongoing use. It can be contended that physicians may condone an occasional short cycle by a recreational athlete – for example, once every 1 or 2 years, provided that the risk of escalating use and addiction is low.

CONCLUSION

Future research should search for methods by which damage caused by androgens can be moderated. Under the assumption that androgen abuse has deleterious effects on health, it could be beneficial to impel athletes to use less androgens than they would do without an intervention. Obviously the most desirable outcome for a clinician or healthcare worker would be to intercept androgen abuse by an athlete entirely, i.e. primary prevention. This is currently endeavored by antidoping organizations with large-scale education programs and restrictive regulations. These measures could surely be effective but will never rule out androgen abuse by a still sizeable group of strength athletes. Secondary prevention could therefore be complimentary and may take the form of harm reduction strategies, for instance the face-to-face counseling of current users by health professionals and education through online discussion forums [21]. A well designed trial that investigates the efficacy of a harm reduction strategy is needed to determine whether such an approach could be put into practice.

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- ■ of special interest
- ■■ of outstanding interest

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