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Anabolic steroids and cardiovascular risk: A national population-based cohort study

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ABSTRACT

Background: Non-therapeutic use of anabolic androgenic steroids (AAS) has been associated with various adverse effects; one of the most serious being direct cardiovascular effects with unknown long-term consequences. Therefore, large studies of the association between AAS and cardiovascular outcomes are warranted. We investigated cardiovascular morbidity and mortality in individuals who tested positive for AAS.

Methods and results: Between 2002 and 2009, a total of 2013 men were enrolled in a cohort on the date of their first AAS test. Mortality and morbidity after cohort entry was retrieved from national registries. Of the 2013 individuals, 409 (20%) tested positive for AAS. These men had twice the cardiovascular morbidity and mortality rate as those with negative tests (adjusted hazard ratio (aHR) 2.0; 95% confidence interval (CI) 1.2–3.3). Compared to the Swedish population, all tested men had an increased risk of premature death from all causes (standardized mortality ratio for AAS-positive: 19.3, 95% CI 12.4–30.0; for AAS-negative: 8.3, 95% CI 6.1–11.0).

Conclusion: Non-therapeutic exposure to AAS appears to be an independent risk factor for cardiovascular morbidity and premature death.

1. Introduction

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone initially developed for clinical purposes (Woerdeman and de Ronde, 2011), but have received attention for their association with doping among athletes. Today, the non-therapeutic use of AAS has become a substantial problem among young recreational exercisers (Dunn and White, 2011). The reported population lifetime prevalence of AAS use in males varies between 1% and 5% in Western countries (Thiblin and Petersson, 2005) but may be much higher in selected settings, such as gyms (Mattila et al., 2010) or prison populations (Klotz et al., 2010). A strong association exists with weight training, even among people without competitive ambitions. AAS use has also become increasingly common among substance abusers (Petersson et al., 2010) and criminals (Klotz et al., 2007, 2010; Lundholm et al., 2010; Skarberg et al., 2010).

AAS use has been associated with a variety of psychiatric and somatic side effects. Some of these side effects are common, such as acne, testicular atrophy with reduced sperm count, and skin edema (Quaglio et al., 2009). Suggested mental side effects include aggressive behavior during use and depression after discontinuation (Thiblin and Petersson, 2005). Consequently, AAS abuse has been linked to violent crimes (Beaver et al., 2008; Lundholm et al., 2010; Pope and Katz, 1990; Skarberg et al., 2010) and suicide (Brower et al., 1989; Thiblin et al., 1999), although a direct causal relationship is uncertain.

Adverse cardiovascular effects are the most frequently reported among the suggested severe, potentially life-threatening, undesired consequences of AAS use. A number of case reports have described myocardial infarction in young AAS users (Thiblin and Petersson, 2005), and several echocardiography studies of AAS users have indicated that long-term AAS use may be linked to left ventricular hypertrophy and cardiac dysfunction, such as impaired ventricular inflow (Baggish et al., 2010). An association between use of AAS and cardiac hypertrophy has also been demonstrated in a study on deceased AAS users (Far et al., 2011). However, other studies have failed to demonstrate substantial effects of AAS on

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cardiac function (Zuliani et al., 1989; Palatini et al., 1996; Thompson et al., 1992; Hartgens et al., 2003; Hajimoradi and Kazerani, 2013). Indirect evidence of an increased risk of ischemic events has been provided by observational and experimental studies associating AAS use with atherogenesis, thrombogenesis, vasospasm, and endothelial dysfunction (Thiblin and Petersson, 2005; Maravelias et al., 2005). Direct cardiotoxic effects resulting in electrocardiographic disturbance have also been reported (Maior et al., 2013) and may result in contractile myocardial dysfunction (Baggish et al., 2010) and increased susceptibility to ischemic injury. However, the importance of non-symptomatic changes, such as left ventricular hypertrophy and endothelial dysfunction, remain controversial, and the mechanisms behind the possible effects of AAS on the heart are poorly understood (Angell et al., 2012).

Therefore, current understanding of the consequences of AAS use on cardiovascular risk is based primarily on indirect evidence and small observational studies (Angell et al., 2012). No large-scale epidemiological studies with long-term follow-up have investigated the potential association between AAS and cardiovascular events. The purpose of the present study was to estimate the association between non-therapeutic exposure to AAS and cardiovascular mortality and morbidity by means of long-term follow-up in a national cohort of men tested for AAS use.

2. Subjects and methods

2.1. Study population

All individuals tested for AAS at the Doping Laboratory at Karolinska University Hospital/Huddinge in Sweden who had a valid personal identification number and test date were enrolled in the cohort. Most individuals had their first test performed between 2002 and 2009. This laboratory was the only Swedish laboratory performing AAS analysis until January 1, 2008. Thereafter, analyses requested by the police were referred to the toxicological laboratory of the Swedish National Board of Forensic Medicine. Urine samples were provided by health care, police, prison and probation service, or customs. Doping tests of athletes performed by sports authorities do not contain personal identification numbers and, consequently, were not included in the study. The dates and results of the tests were combined with information from the national hospital discharge registry (Ludvigsson et al., 2011) and national cause of death registry using the unique personal identification numbers for person-based linkage (Ludvigsson et al., 2009). Individuals younger than 14 years ($n = 2$) or older than 55 years ($n = 13$) at the time of their first test were excluded from the cohort. The upper age limit was used to minimize the risk of including subjects who started to use AAS to counteract physical or sexual impairment, such as older men with short-term exposure. Women were excluded from the study because only 2.1% of the AAS-positive individuals were female. The study was approved by the regional ethical review board in Uppsala, Sweden.

2.2. Definition of AAS exposure

Testing positive for AAS at least once was defined as exposure. Testing negative for AAS at all times during the entire follow-up period was defined non-exposure. Exposure was also categorized according to the number of positive tests.

2.3. Definitions of outcomes

Cardiovascular events were defined as either a hospital episode with a diagnosis indicating a cardiovascular disorder (ICD-9 codes 39*–43*, 441–447, or 451–453 or ICD-10 codes I0*–I7* or I80-I82) that occurred after the first test for AAS, or an underlying cause of death from ICD-10 chapter IX. All-cause mortality was determined from the date of death in the cause of death registry.

2.4. Covariates

Age was used as the time scale in the time-dependent Cox regression analyses. An ecological variable indicating one of three different categories of socioeconomic status was defined based on the proportion of the population eligible for university education within each municipality. A proportion below the 30th percentile was categorized as low, a proportion above the 70th percentile as high, and all others as medium. These categories were assigned to each subject based on their residency. Country of birth was categorized as Sweden, European, or Non-European. AAS users have a propensity for concomitant abuse of other substances (McCabe et al., 2007). Alcohol-related disease (ICD-9: 291, 303, or 980; ICD-10: F10, T51, or X65) or substance abuse (ICD-9: 292, 304, 305, or 967–970; ICD-10: F11–F16, F18, F19, T40, X61, or X62) as indicated at hospital discharge or as cause of death were regarded as potential confounders in the multivariable analyses based on the assumption that these two variables are likely to be associated with AAS use and have a direct impact on the outcome (i.e., cardiac disease). Information on deaths related to alcohol or narcotics was retrieved from death certificate data. Individuals who use AAS also report irritability and depression/suicidal ideation as side effects (Thiblin and Petersson, 2005) and exhibit increased risk taking behavior (McCabe et al., 2007; Middleman et al., 1995). Hospital admissions for psychiatric disease or injury were also extracted from the data. A main cause of death from ICD-10 chapter XIX was considered to be caused by injury. Indicator variables were also defined for the principal hospital discharge diagnoses indicating injury (ICD-9 codes: 8**–9**; ICD-10 codes: S**–T**) or psychiatric disorders (ICD-9 codes: 29*–31*; ICD-10 codes: F**). Causes of injury and intentionality were derived from ICD-10 coding of external causes and classified according to the matrix developed by the National Center for Health Statistics, Centers for Disease Control, USA (MMWR, 1997). Psychiatric disease and injury were explored in univariate analyses but not considered appropriate to adjust for in the multivariable analyses. Psychiatric conditions and risk taking behavior, as reflected by these variables, could be risk factors for non-therapeutic AAS use, but they could also be caused by AAS exposure. Because an individual who tests positive for AAS many times may have been exposed long before the positive test, adjusting for such factors would be difficult. The univariate analysis also explored hospitalizations for cardiovascular disorders prior to testing positive for AAS, but they were not considered to influence exposure status and unlikely to confound the result.

The registries used in the present study do not contain data on smoking, thus making it impossible to control for that possible confounder.

2.5. Statistical analysis

For time to event analyses, person-time accumulated from the date of the first AAS test until an event or censoring on December 31, 2009. Events were defined sequentially as (a) deaths other than those caused by cardiovascular disorders or (b) cardiovascular events. For analysis of cardiovascular events, censoring was also done at the time of death from other causes.

By using gender and chronological 5-year age categories and annual calendar periods from 2002 through 2009, we created a contingency table of the observed number of deaths in the study population. Similarly, accumulated person-time for the corresponding gender, age groups, and calendar periods were calculated. The expected number of deaths was calculated by multiplying the age, gender, and time-specific person-times with the corresponding