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ORIGINAL RESEARCH

Risk of Central Serous Chorioretinopathy in Male Androgen Abusers

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ABSTRACT

Introduction: Male gender is an important risk factor of central serous chorioretinopathy (CSC), and studies have explored the pathophysiological role of androgens in CSC with conflicting results. In this study, we shed light on this hot topic by exploring the risk of CSC in a large cohort of male androgen abusers.

Methods: This study included male androgen abusers identified through a nationwide anti-doping test program across Danish fitness centers from January 3 2006 to March 1 2018. For each case, we randomly sampled ten male controls using Danish nationwide registries. These controls were matched in age and date. Cases and controls were followed until May 16 2018. Data on diagnoses were extracted using the Danish National Registry of Patients using ICD-10 codes to identify cases with CSC.

Results: We included 1189 cases and 11,890 controls. Mean age at the time of doping sentence was 27.4 ± 6.9 years, and mean length of follow-up was 15.8 ± 3.6 years. We identified no cases of CSC in androgen abusers, and five cases of CSC in the control cohort. The difference between groups was not statistically significant ($P = 1.0$).

Conclusions: Male androgen abusers were not at increased risk of CSC. Considering the lack of any signal in this large study, we speculate that if male androgen plays any direct role in the pathophysiology of CSC, its role may be subtle at best.

Keywords: Central serous chorioretinopathy; Androgen abusers; Anabolic steroids; Testosterone; Cohort study

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Key Summary Points

Why carry out this study?

Central serous chorioretinopathy is a common cause of vision loss in men aged 30–60 years.

Studies have explored the pathophysiological role of androgens in central serous chorioretinopathy with conflicting results.

What was learned from the study?

This large study of male androgen abusers gives insight into the risk of central serous chorioretinopathy when individuals are exposed to very high levels of androgens.

Androgen abusers were not at increased risk of central serous chorioretinopathy. If male androgens play any direct role in the pathophysiology of central serous chorioretinopathy, its role may be subtle at best.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a common cause of vision loss among men aged 30–50 years [1]. It is considered the fourth most common maculopathy after neovascular age-related macular degeneration, diabetic macular edema, and retinal venous occlusion [2]. Patients with CSC typically complain of blurred central vision, metamorphopsia, disturbed color perception, and may experience a hypermetropic change in their refraction. Clinically, macular optical coherence tomography reveals subretinal fluid and a thick choroid [3, 4]. Prolonged presence of subretinal fluid should be avoided as irreversible vision loss can occur due to photoreceptor atrophy [5, 6]. A range of treatment modalities aim to provide resolution of subretinal fluid, of which the most popularly used is the half-dose photodynamic therapy (PDT) due to its efficacy and safety [7, 8].

The CSC pathophysiology remains incompletely understood, but clinical findings of dilated choroidal vessels, anastomoses, and vascular hyperpermeability point to a venous overload hypothesis [3, 9], which has also been linked to a thicker sclera [10, 11]. Exposure to corticosteroids is a strong risk factor for CSC [12]. Male sex is another strong risk factor for CSC [9, 13]. Schellevis et al. [14] reported increased levels of steroid hormones that are considered precursors of testosterone in patients with CSC. Studies are conflicting in their findings of testosterone levels, and it remains unclear if testosterone is indeed higher in patients with CSC [15–20].

In this large study, we investigated if male androgen abusers, i.e., individuals with exogenous exposure of extremely high level of androgens, are at increased risk of CSC. For this aim, we used a well-described Danish nationwide retrospective cohort study on male androgen abusers. Androgens play an important role in muscle growth and androgen abuse has therefore been a relatively prevalent issue among athletes and bodybuilders for many years [21]. It is estimated that the prevalence of androgen abuse in males is ~6% [21]. Unfortunately, androgen abuse also leads to hormonal disturbances, gynecomastia, testicular dysfunction, infertility, and cardiomyopathy [21].

METHODS

Study Design

Anti Doping Danmark is a Danish public independent institution with reference to the Ministry of Culture, with the aim of promoting the fight against doping in sport. Their activities include doping control, results management and prosecution, information and education, research in relation to doping, international cooperation in the fight against doping, and assistance to public authorities.

Since 2006, as part of a political ambition to create a safe fitness environment in Denmark, a

total of 342 fitness centers (covering 80% of all fitness center members) collaborated with Anti Doping Danmark in their conduct of ~1000 inspections in these centers annually. The doping inspectors primarily tested individuals suspected of androgen abuse. A positive test, or refusal of participation, led to an immediate 2-year doping sanction and suspension of membership in any of the collaborating fitness centers [21].

This cohort of male androgen abusers has allowed important large-scale health studies to understand the consequences of anabolic steroid abuse [21–24]. Approval was obtained by the Danish National Board of Health (FSEID-00003570) and the Danish Data Protection Agency (2012-58-0004/BFH-2017-105/05949). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Study Participants

From January 3 2006 to March 1 2018, sanctions were given to a cohort of male fitness center members due to androgen traces in urine samples. Another cohort of male fitness center members were sanctioned due to refusal of urine sample delivery, even though they were informed that this would result in an equivalent doping sanction. Studies of these cohorts have confirmed the validity of androgen abuse in the latter group as they exhibit similar rates of side effects that can be directly attributed to androgen abuse, e.g., low fertility and gynecomastia [25].

For each case, we randomly sampled ten age-, gender-, and date-matched control individuals. For example, a male anabolic steroid abuser born in 1987 who tested positive on May 6 2012, would be matched with ten randomly sampled controls from the same birth cohort living in Denmark at that date.

Registries

All residents in Denmark have a unique personal identification number (in Danish *Central Person Register*, CPR) that is used as a general means of identification in relation to all contacts with the public administration and healthcare system [25, 26]. We cross-referenced the patients' CPR numbers with the Danish Civil Registration System [25, 26] and the Danish National Registry of Patients [25, 27], specifically looking for the International Classification of Diseases-10 code H35.7 *separation of retinal layers*, H35.7A *detachment of the retinal pigment epithelium*, and H35.7B *central serous chorioretinopathy*.

Diagnosis of CSC

In Denmark, all citizens have the right to access a primary care ophthalmologist though the public healthcare system, free of charge [25]. The primary care ophthalmologists do not have access to fluorescein and/or indocyanine green angiography for diagnosis, and cannot provide PDT treatment. Thus, cases with CSC are often immediately referred to a hospital department. Ophthalmologists with special interest or experience in medical retina may consider initial observation as some with acute CSC can spontaneously regress [2]. Nationwide registration of ICD-10-based diagnosis codes are mandatory for cases diagnosed at a hospital department, but not available for cases diagnosed at the primary case ophthalmologist [25].

Data Analysis

For descriptive data, continuous variables are presented using mean and standard deviation if normal distribution was present, otherwise using nonparametric descriptive statistics. Categorical variables are presented using numbers and percentages. Incident rate of CSC during the follow-up period was reported in numbers and percentages. We calculated 95% confidence limits (95% CI) for the percentages using the Clopper–Pearson's confidence interval, which is better suited for small numbers [28]. Risk of CSC in androgen abusers compared with controls were explored using odds ratio (OR) with 95% confidence intervals (95% CI). We used a statistical significance threshold of 0.05. As a sensitivity analysis, we separately analyzed cases

with confirmed androgen traces and cases with refused urine sample delivery. All statistics were computed in SAS 9.4 using the proc freq algorithm.

RESULTS

A total of 545 men were sanctioned due to androgen traces in their urine samples, and 644 men were sanctioned because of refused urine sample delivery. Thus, in total 1189 androgen abusers and suspected androgen abusers were included in this study. Our 1:10 sampling of matched control individuals led to 11,890 control individuals. Thus, this cohort included data on 13,079 individuals. Mean age at the time of doping sentence was 27.4 ± 6.9 years among cases, which was matched to the age at enrollment of the control cohort. Similarly, average length of follow-up was 15.8 ± 3.6 years among cases, which was matched with the length of follow-up in the control cohort. Characteristics of cases and controls are summarized in Table 1.

During this long follow-up period, we identified five cases belonging to the ICD-10 group H35.7 *separation of retinal layers,* all within the subcategory H35.7B *central serous chorioretinopathy* among the male controls. We found 0 cases in the cohort of androgen abusers. The estimated OR was 0.0 (95% CI 0.0–7.6). These numbers are outlined in more detail in Table 2.

Sensitivity analyses, in which we focused on cases with confirmed androgen traces and cases with refused urine sample delivery, did not alter the conclusions since none of the cases developed CSC.

Table 1 Characteristics of cases and controls

	Cases	Controls
Number	1189	11,890
Age at time of doping sentence	27.4 ± 6.9 years	27.4 ± 6.9 years
Length of follow-up	15.8 ± 3.6 years	15.4 ± 4.2 years

Data are presented in mean ± standard deviation

DISCUSSION

This is the first study to investigate the risk of CSC among male androgen abusers. To our best knowledge, no other similar studies exist. One publication exists of a case series of nine patients with CSC from two institutions, which were also under exogenous testosterone therapy [29]. Interestingly, two of these patients discontinued testosterone therapy and experienced resolution of subretinal fluid [29]. In that

Table 2 Incident number of diagnoses during follow-up

	Cases		Controls			
	N	% (95% CI)	*N*	% (95% CI)	OR (95% CI)	*P*-value
H35.7 *separation of retinal layers*	0	0.00 (0.00–0.32)%	5	0.04 (0.01–0.1)%	0.0 (0.0–7.6)	1
H35.7A *detachment of the retinal pigment epithelium*	0	0.00 (0.00–0.32)%	0	0.00 (0.00–0.03)%	N/A[a]	N/A[a]
H35.7B *central serous chorioretinopathy*	0	0.00 (0.00–0.32)%	5	0.04 (0.02–0.10)%	0.0 (0.0–7.6)	1

95% CI 95% confidence interval, *%* percentage, *OR* odds ratio, *N* number, *N/A* not available
[a]We could not calculate a meaningful OR since incidence was 0 in both cases and controls

regard, it should be noted that the natural history of CSC exhibits waxing and waning [2, 8], which is why a control group is necessary to fully conclude if an intervention is significantly better than observation [8].

In this large-scale study with a long follow-up, we were unable to find a strong signal that suggests a robust direct pathophysiological link between androgen exposure and CSC. To our great surprise, we observed zero events of CSC in this cohort of androgen abusers, who otherwise have a high prevalence of side effects that can be linked directly to the pharmacodynamics of these drugs. Although theoretically, this study cannot completely rule out a role for androgens, we would expect a stronger signal if testosterone played a direct role in the CSC pathophysiology. In a comprehensive study of the choroid using immunohistochemistry, Brinks et al. [30] demonstrated that the glucocorticoid receptor was highly expressed in the human choroid, whereas minimal expression was found for the androgen receptors. This may seem puzzling considering that male gender is a strong risk factor of incident CSC. One hypothesis for the gender difference may be explained by looking at anastomoses elsewhere. Dural arteriovenous fistulas are pathological anastomoses that lead to venous hypertension and tissue edema [31]. This condition is more prevalent among males and exhibits worsening upon administration of corticosteroids [31]. Another example includes surgically created arteriovenous shunts for hemodialysis in kidney disease [32]. Success of these shunts demonstrate a high gender preference; they are more likely to be successful among males [32, 33]. Thus, taken together, it may be that males are more prone to the development of vascular anastomoses [9], and that sex hormones are innocent bystanders that have gained disproportional focus due to the role of another group of steroids: the corticosteroids [12].

Limitations of this study should be acknowledged when interpreting its results. First, studies of drug abuse are notoriously difficult due to a range of ethical and practical reasons [34]. Our cases were partly based on individuals without urine sample confirmation but were otherwise suspected of being androgen abusers. Although one limitation is that we cannot confirm their androgen abuse, we have previously shown that this cohort develops known adverse effects to androgen abuse at a similar rate as those with confirmed androgen abuse [21]. However, we do not have information on the duration or the exact dose of the androgen abuse, which is an important limitation. Second, our study is based on the confirmed diagnosis of CSC, which requires the patient to develop symptoms and then seek an ophthalmologist. Further, to obtain a diagnosis of CSC in the registries, the ophthalmologist must have referred the patient to the hospital. Although we do not expect the case cohort and the control cohort to be exposed to a systematic bias in terms of access to ophthalmic care, this should be kept in mind as a theoretical source of bias. Further, the referral patterns for CSC changed in 2019 due to worldwide shortage of verteporfin [35]. However, this aspect cannot be considered a source of bias as we stopped our follow-up in May 2018. Third, our cases were active athletes whereas controls were a matched sample of the population; and we were not able to match based on lifestyle choices. Considering that physical activity may protect against depression, anxiety, and sleep disturbances [36], which in turn may influence corticosteroid levels, one can speculate that physical activity may protect against CSC. On the other hand, Piccolino et al. [37] recently reported that vigorous physical activity is a significant risk factor for the development of CSC. Similarly, one can also speculate that athletes may be more aware of their lifestyle beyond physical activity, i.e., diet, smoking, caffeinated drinks. These factors may influence on the risk of CSC [38, 39]. Since androgen abusers may be more fit than the general population, one can also speculate that they are less likely to receive exogenous glucocorticoids, i.e., treatment with corticosteroids. Thus, there is a theoretical source of bias that increases the likelihood of the control cohort to have a higher incident CSC. Finally, CSC typically presents at age 30–60 years, and our study sample of males aged 27.4 ± 6.9 years followed for 15.8 ± 3.6 years is in a relevant age interval albeit in the younger end of the interval. Our

findings may not necessarily be generalizable to androgen abusers aged 50–60 years.

In conclusion, in this large study, we do not find that male androgen abusers are at increased risk of CSC. Our study does not support the notion that testosterone plays a major role in CSC pathophysiology. Further studies are warranted in how male sex is a risk factor for CSC.

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Compliance with Ethics Guidelines. This study was approved by the Danish National Board of Health (FSEID-00003570) and the Danish Data Protection Agency (2012-58-0004/BFH-2017-105/05949). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available to preserve patient confidentiality. The author will on request detail the restrictions and any conditions under which access to some data may be provided.

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