Elevated Steroid Hormone Levels in Active Chronic Central Serous Chorioretinopathy

Rosa L. Schellevis,[1] Lebriz Altay,[2] Asha Kalisingh,[1] Timo W. F. Mulders,[1] Vasilena Sitnilska,[2] Carel B. Hoyng,[1] Camiel J. F. Boon,[3,4] Joannes M. M. Groenewoud,[5] Eiko K. de Jong,[1] and Anneke I. den Hollander[1,6]

[1]Department of Ophthalmology, Donders Institute of Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands
[2]Department of Ophthalmology, University Hospital of Cologne, Cologne, Germany
[3]Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Ophthalmology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
[5]Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands
[6]Department of Human Genetics, Donders Institute of Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence: Anneke I. den Hollander, Radboud University Medical Center, Department of Ophthalmology, Philips van Leydenlaan 15, Route 409, Nijmegen 6525 EX, The Netherlands; anneke.denhollander@radboudumc.nl.

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Purpose. Chronic central serous chorioretinopathy (cCSC) is characterized by fluid accumulation between photoreceptors and the retinal pigment epithelium of which the cause is unknown. Associations with steroid use, stress, pregnancy, and the male sex suggest a role for the steroid hormone system in the disease. Here, we performed a comprehensive analysis of the steroid hormone system in active cCSC.

Methods. Serum hormone levels of 17 steroid hormones were measured in 46 male Caucasian patients with active cCSC and 46 male Caucasian age-matched controls using the AbsoluteIDQ stero17 kit.

Results. Elevated levels of androsterone, estrone, etiocholanolone, and androstenedione were observed in cCSC patients compared with controls. Median hormone levels in cCSC patients versus controls, respectively, were as follows: androsterone, 0.84 ng/mL (interquartile range [IQR] = 0.61–1.06) versus 0.69 ng/mL (IQR = 0.48–0.96, $P = 0.031$); estrone, 0.12 ng/mL (IQR = 0.10–0.15) versus 0.10 ng/mL (IQR = 0.08–0.11; $P = 0.0048$); etiocholanolone, 0.19 ng/mL (IQR = 0.15–0.29) versus 0.13 ng/mL (IQR = 0.099–0.20, $P = 0.0061$). Mean levels of androstenedione were 3.10 ng/ml (SD = 1.03) versus 2.55 ng/mL (SD = 0.95), in cCSC patients versus controls, respectively. Additionally, Spearman's correlations between aldosterone and 11-deoxycortisol, androsterone, DHEA, DHEAS, and E1 differed between cCSC patients and controls, as well as between andosterone and E1, and between DHT and 17OHP.

Conclusions. We present a comprehensive overview of the status of the steroid hormone system in active cCSC. Levels of four hormones were elevated in cCSC patients compared with controls, and the relationships between steroid hormones was altered, indicating that the balance in the steroid hormone system is altered in cCSC patients.

Keywords: central serous chorioretinopathy, steroid hormone, cCSC

Central serous chorioretinopathy (CSC) is a multifactorial retinal disease characterized by fluid accumulation between the photoreceptors and the RPE, leading to vision impairment.[1–3] The etiology of CSC is currently unknown, and treatment options are limited. Two main forms of CSC have been described: acute CSC and chronic CSC (cCSC). Acute CSC usually resolves spontaneously, whereas patients with cCSC have persisting complaints or multiple recurrent episodes of fluid accumulation accompanied with permanent loss of visual acuity and more extensive atrophic RPE alterations.[1,3] CSC is more frequent in men (~80% of patients) and has been associated with stress, the use of steroids, type A personality, and pregnancy,[1–3] suggesting an important role for the steroid hormone system in the disease.

Steroid hormones regulate a large number of physiologic processes, such as sex differentiation, metabolism, and immune responses.[4] To date, only a limited number of studies have investigated hormone levels in CSC patients. The most widely studied hormone in CSC is cortisol, with more than 11 published studies,[5–15] aldosterone was measured in 2 studies,[7,16] testosterone levels were measured in 4 studies,[6,7,9,11] and dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) were both described in only one study each.[7,17] However, results between studies regarding significant associations of cortisol or testosterone levels with cCSC were not consistent, showing associations in some studies but not in others.[5–15] Notably, these studies focused only on a limited number of hormones, whereas it is known that many complex interactions exist between steroid hormones and that they are

highly correlated.[4] A comprehensive analysis of the steroid hormone system would not only provide information on differences in individual steroid hormone levels but would also allow for the assessments of interactions between hormones.

Therefore, to better understand the role of the hormone system and to observe possible imbalances in this system in cCSC, we performed a pilot study in which we simultaneously measured 17 different steroid hormones in serum samples of 46 patients with active cCSC and 46 age- and sex-matched controls. With this comprehensive analysis, we aimed to increase our knowledge on the status of the steroid hormone system in cCSC patients to gain more insight into the mechanisms underlying the disease.

Materials and Methods

Patients and Control Individuals

In this multicenter study, we included 46 Caucasian patients with cCSC from two different university hospitals. As controls, 46 age- and sex-matched Caucasian individuals from the EUGENDA database were used (www.eugenda.org). In total, 16 cCSC patients and 36 controls were collected at the Radboud University Medical Center (Nijmegen, The Netherlands), and 30 cCSC patients and 10 controls were collected at the University Hospital of Cologne (Cologne, Germany). Individuals who reported steroid or eplerenone/spironolactone use within the last 6 months at the moment of blood withdrawal were excluded from the study.

The diagnosis of active cCSC was based on multimodal grading of images obtained via color fundus photographs, optical coherence tomography, fluorescein angiography (FA), and indocyanine green angiography (ICGA) by two independent graders (LA, VS). Active cCSC was defined upon the following criteria[18]: (1) one or more regions of active leakage (focal or diffuse) in FA/ICGA with RPE alterations visible in FA/ICGA, (2) visible subretinal fluid on spectral domain optical coherence tomography (SD-OCT), and (3) subjective visual symptoms and/or SRF on SD-OCT present for at least 6 weeks. Patients with signs of prolonged disease with structural RPE changes such as extensive RPE alterations (≥5 disc areas) and/or intraretinal fluid were excluded. None of the controls and cCSC patients showed signs of other retinal diseases (e.g., drusen, AMD, former or present choroidal neovascularization, myopic degeneration, dome-shaped maculopathy, choroidal hemangioma, vitreomacular traction, and diabetic macular edema) on OCT, fundus photography, or FA/ICGA. Disease duration was a minimal of 2 months for all patients.

Written informed consents were obtained for all individuals participating in this study. This study was performed according to the guidelines of the Declaration of Helsinki and the local ethic committees of the participating hospitals approved the study.

Steroid Measurements

Serum samples were collected using a standardized coagulation and centrifugation protocol, and samples were stored at −80°C within 1 hour after collection. Time of blood withdrawal was recorded for the cCSC patients as they were collected specifically for this study, but was not known for the EUGENDA control samples, which were collected previously for the EUGENDA database. For each participant, an aliquot of frozen serum (500 µL) was shipped to Biocrates Life Sciences (Innsbruck, Austria), and 17 different steroid hormones were measured using the AbsoluteIDQ stero17 assay. The 17 steroids include glucocorticoids (cortisol, cortisone, and 11-deoxycortisol), mineralocorticoids (aldosterone, corticosterone, and deoxycorticosterone [DOC]), progestogens (17α-hydroxyprogesterone [17-OHP] and progesterone), estrogens (estrone [E1] and estradiol [E2]), and androgens (androstenedione, androsterone, dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEAS], dihydrotestosterone [DHT], etiocholanolone, and testosterone). Measurements of the 17 hormones were obtained from Biocrates in an Excel sheet along with a corresponding data report.

Table 1. Demographics and Multimodal Grading of cCSC

	Radboud University Medical Center ($N = 16$)	University Hospital of Cologne ($N = 30$)
Age (mean ± SD)	51.44 ± 8.88	48.77 ± 11.32
Disease duration (mean ± SD)	9.19 ± 8.64	43.80 ± 49.29
Patients with CSC less than 6 mo	9	8
Patients with CSC 6 mo to 1 y	3	5
Patients with CSC more than 1 y	4	17
Leakage type (FA/ ICGA) (*n*)		
One focal hotspot	3	14
≥2 focal hotspots	6	4
Diffuse leakage	9	12
RPE alteration (*n*) (AF/FA/FP)	16	30
Subretinal fluid (*n*) (SD-OCT)	16	30

Statistical Analysis

All statistical analyses were conducted using SPSS (IBM, version 25). Hormone levels in cCSC patients and controls were tested for normality with the Shapiro-Wilk test. Levels of normally distributed hormones were compared between cCSC patients and controls with an independent sample *t*-test, whereas non-normally distributed hormones were tested with a Mann-Whitney *U* test. The levels of associated steroids ($P < 0.05$) were compared between collection sites (Cologne and Nijmegen) with the same tests, depending on the normality of the distribution of the individual hormones. Additionally, levels of the associated steroids were compared between time of blood withdrawal with a Kruskal-Wallis test with the following hourly bins: 0800 to 0900, 0900 to 1000, 1000 to 1200, 1200 to 1300, and 1400 and 1500 hours.

Because all steroid hormones are derived from cholesterol and are thus highly correlated, the Spearman's ρ rank correlation between the different steroid hormones was calculated. The correlation coefficients of cCSC patients and the control individuals were compared by first transforming the ρ correlations into Z-scores using the Fisher Z transformation, and then comparing the differences divided by the SE of the differences to obtain a *P* value as proposed by Cohen et al.[19]

Results

This study included 46 Caucasian male patients with an active episode of cCSC and 46 Caucasian unaffected male controls collected at two university hospitals. The mean age of the included patients was 50 (range, 28–72) years, and the mean age of the age-matched controls was 50 (range, 22–72) years, which was not significantly different. Patient demographics are presented in Table 1.

Fourteen of the 17 steroid hormones were successfully measured, whereas 3 steroids had measurements outside of the

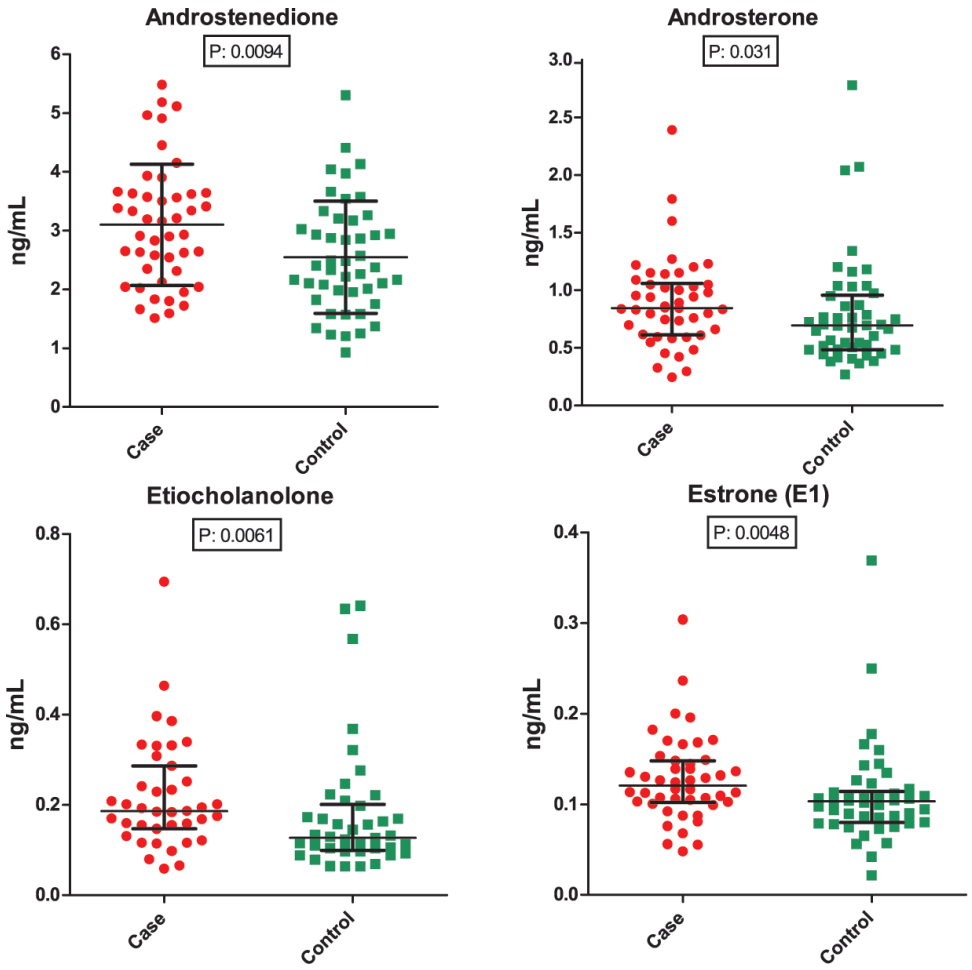

Figure 1. Hormone levels associated with cCSC. The panels indicate the absolute hormone levels measured in cCSC patients (cases) in *red* and controls in *green*. For androstenedione, *error bars* indicate mean and SD, whereas for the other hormones, the median and interquartile ranges are depicted. Values for mean and medians are presented in Table 2.

limit of detection (LOD) in some samples (aldosterone [10 samples; 10.8%], estradiol [E2] [1 sample; 1.1%], etiocholanolone [11 samples; 12.0%]). The distribution of samples that ranged outside of the LOD was equal between cCSC patients and controls. All hormone levels, except for androstenedione, cortisone, and DHEAS, showed deviation from a normal distribution in either cCSC patients or controls; therefore, nonparametric tests were used for these hormones, and median levels with interquartile ranges (IQRs) are described.

Higher levels of androsterone, androstenedione, E1, and etiocholanolone were observed in cCSC patients compared with controls (Fig. 1; Table 2). Median levels for androsterone were 0.84 ng/mL (IQR = 0.61–1.06) in cCSC patients and 0.69 ng/mL (IQR = 0.48–0.96) in controls ($P = 0.031$). The median levels of E1 in cCSC patients were 0.12 ng/mL (IQR = 0.10–0.15) and 0.10 ng/mL (IQR = 0.08–0.11) in controls ($P = 0.0048$). Median concentration of etiocholanolone was 0.19 ng/mL (IQR = 0.15–0.29) in cCSC patients and 0.13 ng/mL (IQR = 0.099–0.20) in controls ($P = 0.0061$). Finally, mean androstenedione levels were 3.10 ng/mL (SD = 1.03) in cCSC patients and 2.55 ng/mL (SD = 0.95) in controls ($P = 0.0094$). Disease duration and age of cCSC patients had no impact on the levels of androsterone, androstenedione, E1, and etiocholanolone ($P > 0.1$ for all). No difference was observed between samples collected from Nijmegen or Cologne for the associated steroids (Supplementary Table S1), and no association was observed between levels of these four steroids and the time of blood withdrawal (Supplementary Table S2).

Next, the relationship between steroids was investigated in cCSC patients and controls by calculating Spearman's ρ correlations between all measured steroids. Numerous steroid hormones were highly correlated in both the cCSC patients and controls (Fig. 2). Comparison of the Spearman's correlation coefficients between cCSC patients and controls identified a difference in correlations for aldosterone with androsterone (0.316 vs. –0.379, $P = 0.00076$), DHEA (0.029 vs. –0.445, $P = 0.019$), DHEAS (0.117 vs. –0.333, $P = 0.031$), E1 (0.381 vs. –0.085, $P = 0.024$), and 11-deoxycortisol (0.208 vs. –0.255, $P = 0.029$) in controls and cCSC patients, respectively. Additionally, a difference in the correlation of androsterone with E1 (0.613 vs. –0.182, $P = 0.014$) and DHT with 17-OHP (–0.100 vs. 0.538, $P = 0.0011$) was observed between controls and cCSC patients, respectively (Table 3; Fig. 2, red bordered squares). The four steroids associated with cCSC were positively correlated in all groups (Supplementary Fig. S1).

Discussion

To obtain a comprehensive overview of the entire steroid hormone system in cCSC, we studied 17 steroids in 46 patients with active cCSC and 46 age-matched controls. We measured elevated levels of androsterone, androstenedione, estrone, and

Table 2. Association Results of Steroids in 46 cCSC Patients Compared With 46 Controls

	Concentration in ng/mL				
	Controls		cCSC Patients		
Non-Normally Distributed Hormones	Median, ng/mL	IQR	Median, ng/mL	IQR	Mann-Whitney *U* 2-Sided *P* Value
11-Deoxy-corticosterone	0.070	(0.053–0.11)	0.088	(0.052–0.13)	0.323
11-Deoxycortisol	0.55	(0.35–0.9)	0.59	(0.41–1.26)	0.492
17α-Hydroxyprogesterone (17-OHP)	2.11	(1.6–2.64)	2.14	(1.63–2.63)	0.854
Aldosterone	0.14	(0.085–0.21)	0.16	(0.13–0.23)	0.303
Androsterone	0.69	(0.48–0.96)	0.84	(0.61–1.06)	**0.031**
Corticosterone	5.12	(3.048–8.49)	4.96	(2.65–9.82)	0.975
Cortisol	259.35	(209.65–360.13)	275.60	(232.05–357.35)	0.331
Dehydroepiandrosterone (DHEA)	10.05	(5.15–15)	11.25	(7.63–16.35)	0.414
Dihydrotestosterone (DHT)	1.28	(1.04–1.73)	1.24	(0.90–1.81)	0.468
Estrone (E1)	0.10	(0.080–0.11)	0.12	(0.10–0.15)	**0.0048**
Estradiol (E2)	0.067	(0.052–0.081)	0.060	(0.052–0.083)	0.654
Etiocholanolone	0.13	(0.099–0.20)	0.19	(0.15–0.29)	**0.0061**
Progesterone	0.17	(0.13–0.26)	0.16	(0.12–0.25)	0.797
Testosterone	14.75	(10.40–18.40)	14.50	(10.8–17.45)	0.587
Normally Distributed Hormones	**Mean, ng/mL**	**SD**	**Mean, ng/mL**	**SD**	**Independent *t*-Test *P* Value**
Androstenedione	2.55	0.95	3.10	1.029	**0.0094**
Cortisone	61.78	16.56	68.01	13.62	0.052
Dehydroepiandrosterone sulphate (DHEAS)	5064.82	3030.96	5759.03	2638.17	0.244

* Bold values indicate statistical significance, $P < 0.05$.

etiocholanolone in patients with active cCSC compared with controls. Additionally, alterations in the balance of the steroid hormone system were observed in cCSC patients, mainly involving relationships of aldosterone with other steroids.

Our study is the first that comprehensively evaluated all 17 steroid hormones in a cCSC case-control cohort. To date, a limited number of studies have been performed on steroid hormone imbalances in cCSC patients, and these studies focused on either single measurements or at most on four steroids simultaneously. Association results were variable between studies and reported hormone levels also varied greatly between studies. Some associations with testosterone, and morning, evening or 24-hour cortisol levels have been reported,[5,7,9,12,14] but other studies did not confirm these results.[9,10,13] Aldosterone, DHEA, and DHEAS were measured, but no associations with cCSC were observed in the studies investigating these hormones thus far.[7,17]

To our knowledge, no studies have been published that have evaluated levels of androsterone, androstenedione, E1, and etiocholanolone in cCSC, and our study is first describing elevated levels of these hormones in cCSC patients. Androsterone, androstenedione, etiocholanolone, and estrone are important products of the sex hormone branch of the steroid hormone system. Androstenedione, androsterone, and etiocholanolone are weak androgens and mainly function as precursors or metabolites for testosterone (Fig. 3).[4] However, androsterone and etiocholanolone have additional neurosteroid properties acting on the $GABA_A$ receptor and are able to cross to the blood–brain barrier to prevent seizures.[20,21] Androstenedione is the main precursor of testosterone and estrone.[4] Estrone is a weak estrogen hormone that can readily be converted to estradiol, has binding affinity to the estrogen receptors ERα and ERβ, and its levels are known to be increased in the blood of postmenopausal women.[22] Currently, the role of these hormones in the etiology of cCSC is still unknown. Future studies might focus on determining the influence of elevated levels of these hormones on the RPE and choroid using for example cell models.

We assessed the steroid hormone system as a whole by investigating relationships between the different hormones. Interestingly, we observed several altered correlations between the measured hormones when comparing controls and cCSC patients. In controls, a positive correlation was observed between aldosterone, androsterone, and estrone. In cCSC patients, a negative correlation for aldosterone with androsterone was observed, and the correlation with estrone with both aldosterone and androsterone was lost. Additionally, in cCSC patients, DHEA, DHEAS, and 11-deoxycortisol were negatively correlated with aldosterone, and DHT was negatively correlated with 17-OHP, whereas these correlations were not observed in controls. Although aldosterone itself was not associated with cCSC in this study, its altered relationship with multiple other hormones suggests an altered balance in the steroid hormone system in cCSC patients. In light of the current clinical trials targeting the mineralocorticoid receptor (the binding site of aldosterone), this observation might be clinically relevant. In future studies, follow-up measurements of patients with active cCSC when they either have spontaneously resolved, have responded to treatment (micropulse laser, photodynamic therapy, or eplerenone) or have persisting complaints might be informative to determine whether alterations in the hormone level balance could be used as predictor of disease status or treatment response, or might in itself be a target for treatment.

In this study, several steps were performed to minimize confounding by factors that are known to influence steroid levels. First, to homogenize the dataset we included only males in this study, because the disease is most prevalent men (9.9:100,000 vs. 1.7:100,000 in women).[23] Because the investigated steroids are product of the sex hormone branch, steroid dysbalance for female cCSC patients should be investigated in future studies. To further homogenize our cohort, the controls used in this study were age-matched with the cCSC patients. Also, all individuals that reported the use of medication containing steroids or used a mineralocorticoid receptor antagonist within the last 6 months prior to blood withdrawal

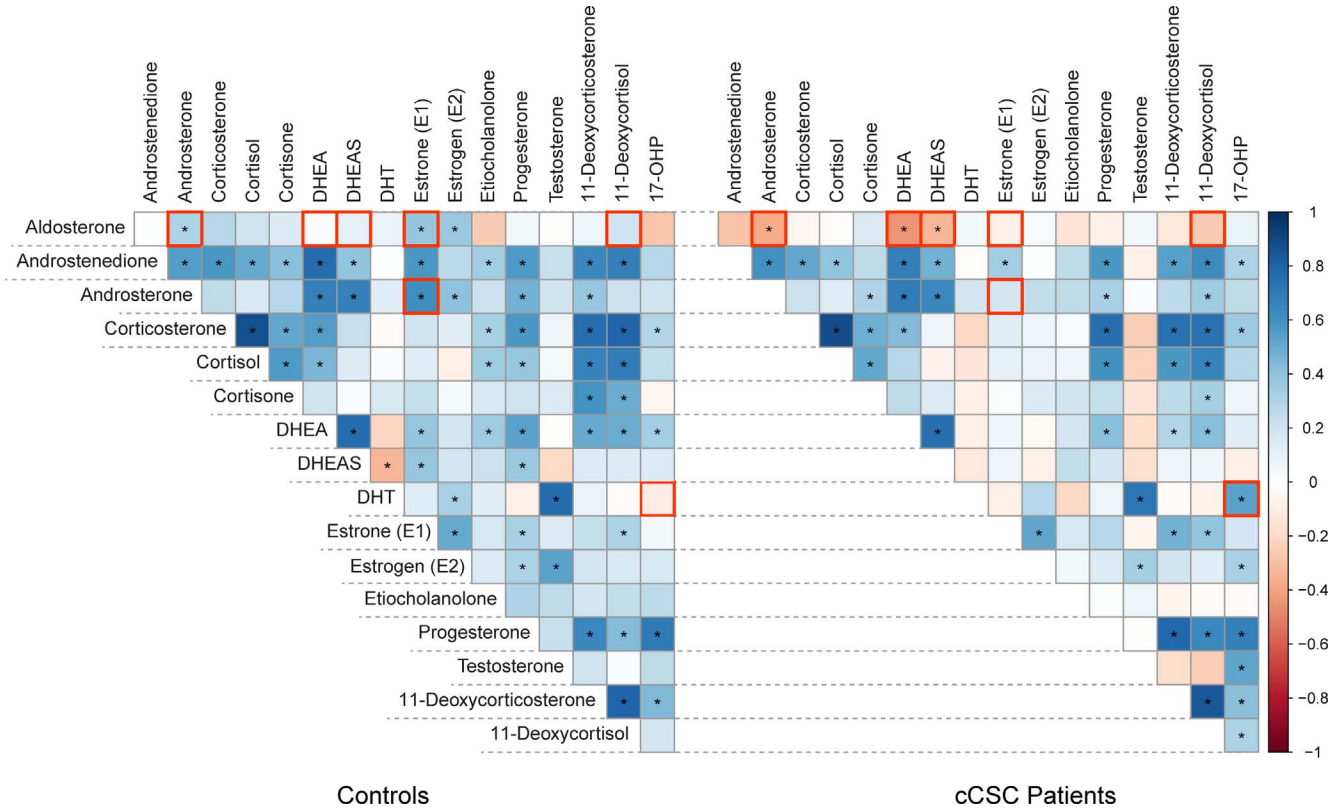

Figure 2. Spearman's correlations between steroid hormones in cCSC patients and controls. *Left:* correlations are depicted as observed in the controls, whereas correlations in cCSC patients are found on the *right*. Colors indicate positive (*blue*) and negative (*red*) correlations between the different hormones, and significant correlations are indicated with an *asterisk. Red bordered squares* highlight correlations that are significantly different between cCSC patients and controls (Table 3).

were excluded. Additionally, we excluded patients that are suspicious for the presence of choroidal neovascularization (CNV), such as patients with intraretinal fluid; however, no OCT angiography was performed. In the future studies, we suggest to extend phenotyping with OCT angiography imaging to exclude possible CNV. Finally, for the cCSC-associated hormones, we confirmed that levels were not dependent on time at blood withdrawal and did not differ between recruitment sites.

Here, by simultaneously measuring 17 components of the steroid hormone system in a group of active cCSC patients, the status of the hormone system could be investigated. This approach allowed us to describe elevated single hormone levels in addition to altered relationships between various hormones in cCSC patients compared with controls. Even though our study is one of the larger studies on steroid measurements in cCSC patients performed to date, the current sample size is still limited, and future studies should focus on replication of the current study in an independent cCSC cohort. Also, as most steroids have a diurnal rhythm, future studies should include both morning and evening samples of the same individual, as well as 24-hour urine measurements. Furthermore, steroid dysbalance should be investigated for acute CSC patients in future studies, as these patients might show different hormonal alterations than chronical patients. Finally, as only male cCSC patients were included in this study, measurements of the 17 steroids and the hormone system balance in female cCSC patients could provide new insights on sex-specific differences in the disease.

Conclusions

In this study, we measured elevated levels of androsterone, androstenedione, E1, and etiocholanolone in Caucasian pa-

Table 3. Difference in Correlations of Steroid Hormones Between cCSC Patients and Controls

	Controls		cCSC Patients				
Correlation	**Spearman ρ**	**Correlation *P* Value**	**Spearman ρ**	**Correlation *P* Value**	**Delta ρ**	**Delta Z**	***P* Value**
Aldosterone-11-deoxycortisol	0.208	0.198	−0.255	0.103	0.463	2.188	**0.029**
Aldosterone-androsterone	0.316	0.047	−0.379	0.013	0.695	3.367	**0.00076**
Aldosterone-DHEA	0.029	0.859	−0.445	0.0031	0.474	2.354	**0.019**
Aldosterone-DHEAS	0.117	0.473	−0.333	0.031	0.450	2.152	**0.031**
Aldosterone-estrone (E1)	0.381	0.0153	−0.085	0.592	0.466	2.255	**0.024**
Estrone (E1)-androsterone	0.613	6.00×10^{-6}	0.182	0.227	0.431	2.456	**0.014**
DHT-17OHP	−0.100	0.510	0.538	1.13×10^{-4}	−0.638	3.255	**0.0011**

* Bold values indicate statistical significance, $P < 0.05$.

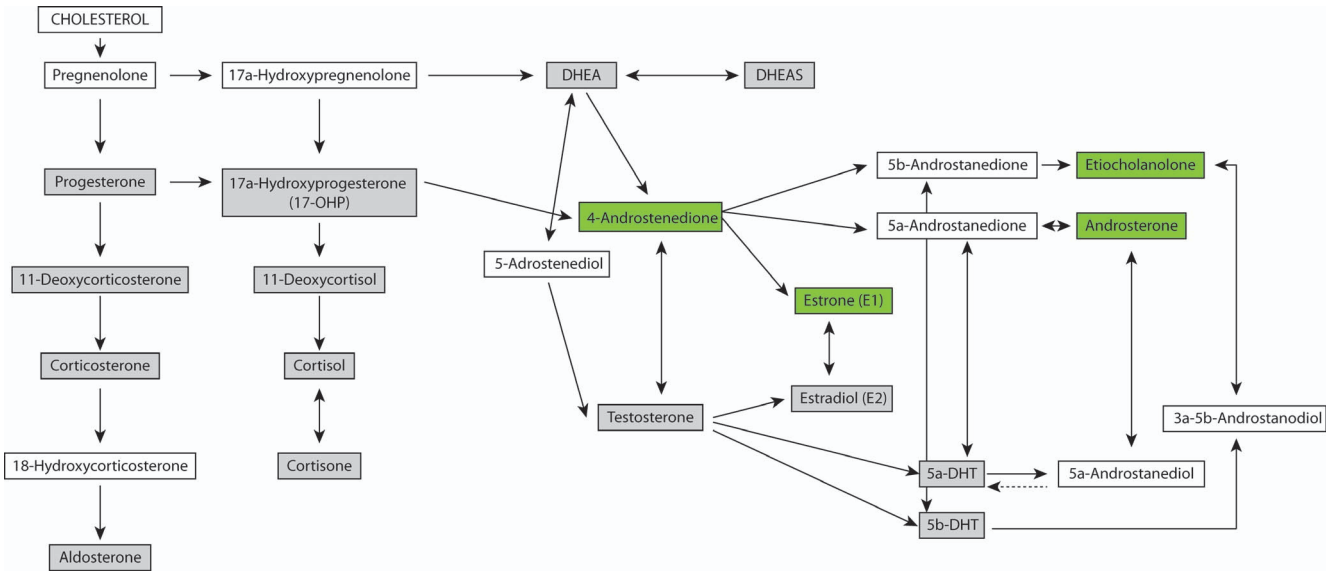

Figure 3. Overview of the steroid hormone pathway and alterations in cCSC. Conversion steps between hormones are indicated with *arrows*. The hormones measured in this study that were not significantly altered in cCSC are indicated as *gray boxes*, whereas *green boxes* indicate significantly elevated hormones levels in cCSC patients. Figure based on Ref. 4.

tients with an active episode of cCSC compared with controls. Additionally, we observed altered correlations between hormones in cCSC patients, mainly with aldosterone, indicative of an altered hormone system balance in individuals with cCSC. This study provides new insights into the status of the steroid hormone system in active cCSC and suggests new leads for future studies into the role of steroid hormones in cCSC. These studies should include larger sample sizes and multiple measure points per patients to evaluate the potential predictive value of the hormone system balance for active phases of cCSC and on whether restoring steroid hormone balance might be an avenue for treatment of cCSC.

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