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Adrenocortical Hormone Abnormalities in Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Abstract

Objectives— To identify adrenocortical hormone abnormalities as indicators of endocrine dysfunction in CP/CPPS.

Methods— We simultaneously measured the serum concentrations of 12 steroids in CP/CPPS and control patients, using isotope dilution liquid chromatography followed by atmospheric pressure photospray ionization and tandem mass spectrometry.

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Results— Twenty-seven CP/CPPS patients and 29 age-matched asymptomatic healthy controls were evaluated. In the mineralocorticoid pathway, progesterone was significantly higher, whereas corticosterone and aldosterone concentrations were significantly lower, in CP/CPPS than in controls. In the glucocorticoid pathway, 11-deoxycortisol was significantly lower, and cortisol concentrations were not different between patients and controls. In the sex steroid pathway, androstenedione and testosterone concentrations were significantly higher in CP/CPPS than in controls. Estradiol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) concentrations were not different between patients and controls. NIH-CPSI total and pain domain scores correlated positively with 17-hydroxyprogesterone and aldosterone ($P<0.001$) and negatively with cortisol concentrations ($P<0.001$).

Conclusions— Results suggest reduced activity of CYP21A2 (P450c21), the enzyme that converts progesterone to corticosterone, and 17-hydroxyprogesterone to 11-deoxycortisol. Furthermore, these results provide insights into the biological basis of CP/CPPS. Follow-up studies should explore the possibility that CP/CPPS patients meet the diagnostic criteria for nonclassical CAH and if hormonal findings improve or worsen in parallel with symptom severity.

Keywords

chronic prostatitis with chronic pelvic pain syndrome; adrenal cortex; biological markers

Introduction

The search for an etiology or biomarker for the prevalent and clinically important disease ^{1, 2}, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), has thus far proven elusive. ¹ Evidence suggest the possibility that CP/CPPS symptoms result from a general, systemic condition, not localized prostate infection, inflammation or dysfunction. ² A significant number of CP/CPPS patients report associated cardiovascular, neurological, psychiatric, and immunologic disease; many also meet diagnostic criteria for fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. ³

A variety of vulnerability factors have been implicated for the development of these various systemic conditions, including complex but subtle hormonal abnormalities related to the hypothalamic-pituitary-adrenal (HPA) axis. ⁴ The goal of this study was to investigate and begin to characterize such adrenocortical hormone abnormalities as indicators of endocrine dysfunction in CP/CPPS patients and thereby improve our understanding of the condition and identify potential biomarkers for the disease.

Material and Methods

Design

This was a double-blind biomarker discovery study. Serum samples were obtained from CP/CPPS patients and age-matched healthy asymptomatic controls at two tertiary referral medical centers specializing in the diagnosis of CP/CPPS during 2006. Following subject recruitment and sample collection, all specimens were analyzed in a single batch at a single blinded research institution using isotope dilution liquid chromatography followed by atmospheric pressure photospray ionization and tandem mass spectrometry (LC-APPI-MS/MS). The institutional review boards at the respective institutions approved the study.

Participants

The primary diagnostic criterion for CPPS was pain or discomfort in the pelvic region for at least 3 months of the previous 6 months. Eligible men were required to have at least "moderate"

symptoms, defined as a total NIH-CPSI⁵ score > 15. Eligibility criteria were identical to those of the NIH-CPCRn and are available elsewhere.⁶

Healthy asymptomatic men from the general population were matched to the cases by age and served as voluntary controls. In addition to an NIH-CPSI score of zero, the controls were required to have a prostate-specific antigen level < 2.5 ng/mL and normal digital rectal exam.

Procedure

The study included one clinic visit during which subjects provided written informed consent, completed the NIH-CPSI questionnaire, and provided blood and urine samples. Because of the effect of the circadian rhythm on adrenocortical function,^{7,8} all samples were obtained at the time of peak hormone concentration between 7:00 and 8:00 AM after an overnight fast. To minimize the effect of inter-assay variability, CP/CPPS and control samples were assayed in the same run. Blood samples were centrifuged to separate serum and all samples were frozen at -70°C and stored until shipped and processed.

Simultaneous determination of 12 steroid concentrations

An API-5000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX, Foster City, CA/Concord, Ontario, Canada) equipped with an atmospheric pressure photoionization source, 3 Shimadzu LC-10ADvp pumps, a Shimadzu SIL-HT autosampler, and a Shimadzu DUG-14A degasser (Shimadzu Scientific Instruments, Columbia, MD) employing isotope dilution with deuterium-labeled internal standard for each analyte was used to measure hormone concentrations.⁹ 200 µL of serum was deproteinized by adding 300 µL of acetonitrile containing internal standards. After centrifugation, 450 µL of supernatant was diluted with 900 µL of water, and then injected a 1,000 µL aliquot into the LC-APPI-MS/MS system. After 3 minutes of washing, the steroids were eluted from the column with a water/methanol gradient at a flow rate of 0.6 ml/min, and introduced the sample into the mass spectrometer. Quantitation by multiple reaction monitoring (MRM) analysis in positive ion mode was performed for 11 analytes, and in negative ion mode for aldosterone.

Accuracy of the method was evaluated by: (a) comparing our methods with previously validated MS/MS methods conducted at the Mayo Clinic and (b) performing recovery studies. The results of the comparison study yielded correlations ranging from $r = 0.908$ to 0.999 . Within-day coefficients of variation (CVs) were less than 11.5% for all analytes tested and between-day CVs ranged from 3.5% to 12.2%.

The amount of analyte we recovered was close to the target value spiked into a serum pool. Mean recoveries of the analytes under study ranged from 90% to 110%. The lower limit of detection (LOD = a reading of 3 standard deviations (SD) above baseline noise) for each steroid ranged from 1.5 to 10 pg/ml. We have previously published details of the protocol.⁹

Data analysis

CP/CPPS patients and controls were compared using t-tests, chi-square tests, and Kruskal-Wallis analysis of variance with Scheffé contrasts. Jonckheere's test was employed to analyze trends among the groups. Values were expressed as means $\pm$ SD, unless specified otherwise. For all steroids wherein subject values fell below the limit of detection of the instrument, these values were set at the limit of detection and the groups were compared using the Mann-Whitney nonparametric test. Correlational analyses were conducted using the Spearman Rank Method; p values < 0.05 (two-tailed) were considered statistically significant. All tests were conducted using Version 9.1.3 of the SAS software package (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC 27513).

Results

Twenty seven CP/CPPS patients and 29 age-matched healthy controls were included in the analysis. Three CP/CPPS patients and 4 control subjects were excluded from the final analysis due to multiple values more than 2 SD greater than the mean value for the respective group. No differences in demographic parameters between CP/CPPS cases and controls were identified (Table 1). Patients had an average ($\pm$ SD) of 2.4 ± 1.0 co-morbid disorders in addition to CP/CPPS: nervous in 16 (anxiety, numbness, tingling), allergic in 9 (sinusitis, allergies, asthma), musculoskeletal in 7 (chronic fatigue syndrome, fibromyalgia, arthritis), gastrointestinal in 6 (irritable bowel syndrome), cardiovascular in 7 (hypertension, palpitations, sweating), and other urogenital in 11 (erectile dysfunction, balanitis, stones).

Evaluation of serum adrenocortical hormone concentrations

In the mineralocorticoid synthetic pathway (see Figure 1), concentrations of progesterone were found to be significantly higher in CP/CPPS than in controls, whereas corticosterone and aldosterone were significantly lower in patients than in controls (Table 2).

In the glucocorticoid synthesis pathway (see Figure 1), serum concentrations of 11-deoxycortisol (11-DOC) were significantly lower, and those of cortisol were not different in patients than in controls (Table 2).

In the sex steroid synthetic pathway (see Figure 1), serum concentrations of androstenedione (ASD) and testosterone were significantly higher in CP/CPPS than in controls, whereas those of estradiol were not different. ASD also can be synthesized from dehydroepiandrosterone (DHEA), which also can interconvert with dehydroepiandrosterone sulfate (DHEAS). Serum concentrations of DHEA and DHEAS were not different between CP/CPPS patients and controls (Table 2).

These results suggested reduced activity of CYP21A2 (P450c21), the enzyme that converts progesterone (via 11-deoxycorticosterone, which was not measured in the current study) to corticosterone, and 17-OHP to 11-DOC (Figure 1). To further investigate this possibility, we calculated precursor/product ratios and found them significantly elevated in CP/CPPS patients relative to controls (Table 2).

NIH-CPSI total and pain domain scores correlated positively ($P < 0.001$), with 17-OHP and aldosterone and negatively ($P < 0.001$) with cortisol concentrations (Table 3).

Comment

CP/CPPS patients had abnormally high levels of progesterone and androstenedione, and abnormally low levels of corticosterone, aldosterone, and 11-DOC compared to healthy volunteers. Furthermore, lower levels of cortisol and higher levels of aldosterone were associated with higher pain and CPSI scores. These clinical correlates provide tantalizing insights into the systemic nature of CP/CPPS.

In contrast to traditional assumptions about CP/CPPS—that it is a disease that originates in the prostate,^{10,11} that it is an infectious disease treatable with antibiotics,^{12–14} that it is a psychosomatic disorder with no biological basis²—recent studies have identified a variety of co-morbid disorders in patients with CP/CPPS, suggesting it may be a systemic disorder.³ Our interest in characterizing adrenocortical hormone levels in CP/CPPS was prompted by findings of HPA disturbances in some of these co-morbid conditions.³ The present results confirm the presence of HPA abnormalities in CP/CPPS patients. In particular, the hormonal abnormalities are characterized by an increased concentration of *proximal* adrenocortical hormones and a

corresponding decrease of *distal* hormones within their respective steroidal synthetic pathways (Figure 1). These findings suggest a defect in CYP21A2 (also known as 21-hydroxylase), the enzyme responsible for converting progesterone to deoxycorticosterone (and subsequently corticosterone and aldosterone), and 17-OHP to 11-DOC.

CYP21A2 defects traditionally have been described in patients with congenital adrenal hyperplasia (CAH). The hormonal defects in our CP/CPPS population suggest that some may have an inherited or acquired form of non-classical CAH due to CYP21A2 deficiency. Classical CAH presents with salt wasting or genital ambiguity in infants. In contrast, non-classical (also known as mild or late-onset) CAH is characterized by partial CYP21A2 deficiency and varying signs of hyperandrogenism—abnormalities that are generally thought to be asymptomatic in men.^{15,16} In our study, the CP/CPPS patients also had hormonal evidence of hyperandrogenism, elevated androstenedione and elevated testosterone levels compared to controls, a finding that further supports the presence of reduced CYP21A2 activity. These results suggest that follow-up endocrinological and genetic testing could determine the role of CYP21A2 abnormalities in men with CP/CPPS.¹⁷

Reduced morning cortisol concentrations have been described in several other pain syndromes, including fibromyalgia,¹⁸ some functional gastrointestinal disorders,¹⁹ and low back pain.²⁰ However in our study, unstimulated morning cortisol concentrations were not different between CP/CPPS cases and controls. In women with interstitial cystitis, a condition similar to CP/CPPS, patients with lower morning cortisol had significantly more pain and urgency, and those with lower urinary free cortisol reported more overall symptomatology ($P<0.05$),²¹ although mean urinary or salivary cortisol did not differ between patients and controls.²¹ This negative correlation is similar to that found for serum cortisol in our patients (Table 3). The underlying biological basis for hypocortisolemia in such chronic pain conditions is incompletely understood, and may be a protective adaptation to chronic stress.²²

Although direct measurements of cortisol concentrations were not different between patients and controls in our study, the excess concentrations of progesterone and androstenedione still suggest a relative hypocortisolemia (because reduced negative feedback by cortisol on the corticotrophs of the anterior pituitary gland causes increased adrenocorticotropin [ACTH] secretion that stimulates adrenal hormone steroidogenesis, leading to excess hormone concentrations proximal to the CYP21A2 defect). We could not obtain ACTH measurements in our patients or results from cosyntropin testing in our patients to further investigate this possibility, but if these patients do in fact have hypocortisolemia, it would further implicate a defect in CYP21A2 and an association with non-classical CAH. To test this hypothesis, future prospective cohort studies should measure both morning ACTH and diurnal cortisol concentrations and perform cosyntropin stimulation testing in patients with CP/CPPS.

Limitations of the current study include small sample size, cortisol concentration measurements taken only from morning samples, a cross-sectional design that prevents conclusions about causality, and the lack of measurement of some adrenal hormones due to the unavailability of quantitative MS assays for those substances. Compared to results obtained from immunoassays used routinely in clinical practice, our quantitative results appear to be lower than the traditional reference ranges. This can be explained by the lack of specificity in the traditional assays, which cross-react with molecules of similar structure and result in readings that are higher than those obtained by tandem mass spectrometry. Unlike immunoassays, isotope dilution tandem mass spectrometry is quite specific for the steroids tested and does not quantify other steroids of similar structure (Tables 5–9 in reference 21).²³

Conclusions

The hormonal differences we identified in CP/PPS patients may help us understand the etiology of CP/PPS and/or serve as biomarkers for the disease. Our study suggested that some men with CP/PPS may have a defect in CYP21A2. Future studies should explore the possibility that CP/PPS patients meet the diagnostic criteria for nonclassical CAH due to 21-hydroxylase deficiency by performing a CRF and cosyntropin stimulation test with 17-OHP measurements, and, if confirmatory, DNA testing for CYP21A2 mutations. Follow-up studies should further assess whether the hormonal findings described in this paper improve or worsen in parallel with symptom severity. Finally, if our work is confirmed, consideration may be given to performing a randomized, controlled trial of low-dose dexamethasone (the treatment of choice for patients with CAH) in patients with CP/PPS to assess whether normalization of these hormonal abnormalities improves symptoms.

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References

- Alexander RB. Treatment of chronic prostatitis. *Nat Clin Pract Urol* 2004;1:2–3. [PubMed: 16474440]
- Potts JM. Chronic pelvic pain syndrome: a non-prostatocentric perspective. *World J Urol* 2003;21:54–6. [PubMed: 12819913]
- Pontari MA, McNaughton-Collins M, O'Leary MP, Calhoun EA, Jang T, Kusek JW, Landis JR, Knauss J, Litwin MS. A case-control study of risk factors in men with chronic pelvic pain syndrome. *BJU Int* 2005;96:559–65. [PubMed: 16104910]
- Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. *Annu Rev Physiol* 2005;67:259–84. [PubMed: 15709959]
- Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol* 1999;162:369–75. [PubMed: 10411041]
- Proper KJ, Alexander RB, Nickel JC, Kusek JW, Litwin MS, Landis JR, Nyberg LM, Schaeffer AJ. Design of a multicenter randomized clinical trial for chronic prostatitis/chronic pelvic pain syndrome. *Urology* 2002;59:870–6. [PubMed: 12031372]
- Kage A, Fenner A, Weber B, Schoneshofer M. Diurnal and ultradian variations of plasma concentrations of eleven adrenal steroid hormones in human males. *Klin Wochenschr* 1982;60:659–66. [PubMed: 6289002]
- Andersson AM, Carlsen E, Petersen JH, Skakkebaek NE. Variation in levels of serum inhibin B, testosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin in monthly samples from healthy men during a 17-month period: possible effects of seasons. *J Clin Endocrinol Metab* 2003;88:932–7. [PubMed: 12574235]
- Guo T, Taylor RL, Singh RJ, Soldin SJ. Simultaneous determination of 12 steroids by isotope dilution liquid chromatography–photospray ionization tandem mass spectrometry. *Clin Chim Acta* 2006;372:76–82. [PubMed: 16707118]
- Nickel JC, Alexander RB, Schaeffer AJ, Landis JR, Knauss JS, Proper KJ. Leukocytes and bacteria in men with chronic prostatitis/chronic pelvic pain syndrome compared to asymptomatic controls. *J Urol* 2003;170:818–22. [PubMed: 12913707]
- Lee JC, Muller CH, Rothman I, Agnew KJ, Eschenbach D, Ciol MA, Turner JA, Berger RE. Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls. *J Urol* 1999;161:584–7. [PubMed: 12544312]discussion 587–8, 2003

12. Alexander RB, Probert KJ, Schaeffer AJ, Landis JR, Nickel JC, O'Leary MP, Pontari MA, McNaughton-Collins M, Shoskes DA, Comiter CV, et al. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. *Ann Intern Med* 2004;141:581–9. [PubMed: 15492337]
13. Dimitrakov JD, Kaplan SA, Kroenke K, Jackson JL, Freeman MR. Management of chronic prostatitis/chronic pelvic pain syndrome: an evidence-based approach. *Urology* 2006;67:881–8. [PubMed: 16698346]
14. Nickel JC. The three As of chronic prostatitis therapy: antibiotics, alpha-blockers and anti-inflammatories. What is the evidence? *BJU Int* 2004;94:1230–3. [PubMed: 15610095]
15. Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med* 2003;349:776–88. [PubMed: 12930931]
16. New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2006;91:4205–14. [PubMed: 16912124]
17. Charmandari E, Merke DP, Negro PJ, Keil MF, Martinez PE, Haim A, Gold PW, Chrousos GP. Endocrinologic and psychologic evaluation of 21-hydroxylase deficiency carriers and matched normal subjects: evidence for physical and/or psychologic vulnerability to stress. *J Clin Endocrinol Metab* 2004;89:2228–36. [PubMed: 15126546]
18. Gur A, Cevik R, Sarac AJ, Colpan L, Em S. Hypothalamic–pituitary–gonadal axis and cortisol in young women with primary fibromyalgia: the potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism. *Ann Rheum Dis* 2004;63:1504–6. [PubMed: 15479904]
19. Bohmelt AH, Nater UM, Franke S, Hellhammer DH, Ehlert U. Basal and stimulated hypothalamic–pituitary–adrenal axis activity in patients with functional gastrointestinal disorders and healthy controls. *Psychosom Med* 2005;67:288–94. [PubMed: 15784796]
20. Griep EN, Boersma JW, Lentjes EG, Prins AP, van der Korst JK, de Kloet ER. Function of the hypothalamic–pituitary–adrenal axis in patients with fibromyalgia and low back pain. *J Rheumatol* 1998;25:1374–81. [PubMed: 9676772]
21. Lutgendorf SK, Kreder KJ, Rothrock NE, Hoffman A, Kirschbaum C, Sternberg EM, Zimmerman MB, Ratliff TL. Diurnal cortisol variations and symptoms in patients with interstitial cystitis. *J Urol* 2002;167:1338–43. [PubMed: 11832727]
22. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology* 2005;30:1010–6. [PubMed: 15950390]
23. Guo T, Chan M, Soldin SJ. Steroid profiles using liquid chromatography–tandem mass spectrometry with atmospheric pressure photoionization source. *Arch Pathol Lab Med* 2004;128:469–75. [PubMed: 15043485]

Key of Definitions for Abbreviations (in alphabetical order)

ASD	androstenedione
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
CPC	Chronic Prostatitis Cohort
CPCRN	Chronic Prostatitis Collaborative Research Network
CV	coefficient of variation
DHEA	dehydroepiandrosterone

DHEAS	dehydroepiandrosterone sulfate
HPA	hypothalamic-pituitary-adrenal (axis)
LC-APPI-MS/MS	liquid chromatography-atmospheric pressure photoionization-mass spectrometry/mass spectrometry
MRM	multiple reaction monitoring
MS/MS	tandem mass spectrometry
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
SD	standard deviation
SNS	sympathetic nervous system
11-DOC	11-deoxycortisol
17-OHP	17-hydroxyprogesterone

Biochemical abnormalities in CP/CPPS patients

Figure 1. Normal pathways and adrenocortical biochemical abnormalities in men with CP/CPPS

The first step in adrenal steroid synthesis is the combination of acetyl CoA and squalene to form cholesterol, which is then converted into pregnenolone. The enclosed area contains the core steroidogenic pathway utilized by the adrenal glands and gonads.

21 : 21-hydroxylase (CYP21A2, P450c21); **DHEA** : dehydroepiandrosterone; **DHEAS** : DHEA sulfate.

Table 1
Distribution of Baseline Demographic Characteristics in Controls and Men with CP/CPPS

Characteristic	Controls n (%)	CP/CPPS n (%)	P
Age, years			
< 25	7 (21%)	8 (27%)	P=0.38 [*]
25–34	12 (37%)	12 (40%)	
35–44	9 (27%)	8 (27%)	
45–54	5 (15%)	2 (6%)	
Currently living with partner			
Yes	19 (58%)	22 (73%)	P=0.78 [†]
No	14 (42%)	8 (27%)	
Currently employed			
Yes	24 (73%)	23 (77%)	P=0.56 [†]
No	9 (27%)	7 (23%)	
Cigarette smoking			
Never	18 (55%)	22 (74%)	P=0.50 [‡]
Current	8 (24%)	4 (13%)	
Former	7 (21%)	4 (13%)	
Drink alcohol	21 (64%)	17 (57%)	P=0.59 [†]
Drink caffeine	26 (79%)	16 (53%)	P=0.06 [†]

* Student's unpaired t-test

[†] Fisher's Exact Test

[‡] chi-square test

Table 2
Adrenocortical Hormone Concentrations in CP/CPFS Patients and Healthy Control Subjects

Steroid	units	Reference range [¶]	CP/CPFS Patients(n=27)	Healthy Controls(n=29)	P
Mineralocorticoid Pathway					
Progesterone	ng/dL	13–97	26.2 (1, 290)	1 (1, 3)	0.03 [§]
Corticosterone	ng/dL	100–700	40 (21, 75)	141 (69, 311)	<0.0001 [§]
Aldosterone	pg/mL	20–90	18 (4, 64)	61 (30, 92)	0.02 [§]
Glucocorticoid Pathway					
17-OH Progesterone	ng/dL	50–250	46 (19, 98)	54 (22, 95)	0.61 ^{//}
11-deoxycortisol	ng/dL	20–130	12 (5, 18)	31 (15, 66)	0.0001 [§]
Cortisol	µg/dL	5–21	11.5 ± 1.1	13.3 ± 1.0	0.21 [†]
Sex Steroid Pathway					
Androstenedione	ng/dL	50–250	126 (100, 168)	73 (50, 96)	<0.0001 [§]
Testosterone	ng/dL	260–1000	60 (37, 79)	8 (1, 402)	0.006 [§]
Estradiol	pg/mL	10–50	14 (10, 30)	10 (10, 21)	0.26 [§]
DHEA	ng/dL	160–800	115 (53, 237)	122 (75, 259) [‡]	0.32 [§]
DHEAS	µg/dL	18–30–125–619	115.1 ± 10.4 [*]	110.4 ± 11.7	0.77 [†]
		31–50–59–452			
		51–60–20–413			
Ratios					
Progesterone/Corticosterone			1.3 (0.03, 6.3)	0.01 (0.00, 0.04)	<0.0001 [§]
17-OHP/11deoxycortisol			3.42 (1.53, 11.3)	1.9 (0.60, 4.75)	0.025

* Mean ± SEM

[†] Student's unpaired t-test

[‡] Median (25th percentile, 75th percentile)

[§] Kruskal-Wallis test

^{//} Mann Whitney test

[¶] All reference ranges from the Quest Diagnostics Endocrinology Manual, except for DHEA, progesterone and 11-deoxycortisol, which are from Endocrine Sciences.

Table 3

Correlations between Hormone Concentrations and Total NIH-CPSI and Pain Domain Scores in Men with CP/CPPS.

Steroid	Total NIH-CPSI Score		Pain Domain Score	
	r	P	r	P
Mineralocorticoid Pathway				
Progesterone [†]	-0.31 [†]	0.12	-0.24	0.22
Corticosterone [†]	-0.24 [†]	0.23	-0.35	0.07
Aldosterone[†]	0.78 [†]	<0.0001	0.71	0.0002
Glucocorticoid Pathway				
17-OH Progesterone[†]	0.42 [†]	0.03	0.40	0.04
11-deoxycortisol [†]	-0.22 [†]	0.25	-0.36	0.06
Cortisol[*]	-0.66 [*]	0.0002	-0.62	0.0006
Sex Steroid Pathway				
Androstenedione [†]	-0.12	0.54	-0.13	0.53
Testosterone [†]	-0.24 [†]	0.22	-0.25	0.20
Estrogen [†]	0.02 [†]	0.92	0.07	0.72
DHEA [†]	0.02	0.91 [†]	0.01	0.95
DHEAS [*]	0.33	0.09 [*]	0.28	0.16

* Pearson (parametric)

[†] Spearman (non-parametric)