MEN'S SEXUAL HEALTH

Normal Testosterone but Higher Luteinizing Hormone Plasma Levels in Men With Hypersexual Disorder

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ABSTRACT

Introduction: Hypersexual disorder as suggested to be included in the Diagnostic and Statistical Manual of Mental Disorders-5 integrates aspects of sexual desire deregulation, impulsivity, and compulsivity. However, it is unknown how it affects gonadal activity and the function of the hypothalamus-pituitary-gonadal (HPG) axis.

Aim: The aim of this study was to investigate testosterone and luteinizing hormone (LH) levels in hypersexual men compared with healthy controls. Furthermore, we investigated associations between epigenetic markers and hormone levels.

Methods: Basal morning plasma levels of testosterone, LH, and sex hormone—binding globulin (SHBG) were assessed in 67 hypersexual men (mean age: 39.2 years) compared with 39 age-matched healthy controls (mean age: 37.5 years). The Sexual Compulsivity Scale and the Hypersexual Disorder: Current Assessment Scale were used for assessing hypersexual behavior, the Montgomery-Åsberg Depression Scale-self rating was used for depression severity, and the Childhood Trauma Questionnaire (CTQ) was used for assessing history of childhood adversity. The genome-wide methylation pattern of more than 850 K CpG sites was measured in whole blood using the Illumina Infinium Methylation EPIC BeadChip. CpG sites located within 2,000 bp of the transcriptional start site of hypothalamus pituitary adrenal (HPA) and HPG axis—coupled genes were included.

Main Outcome Measures: Testosterone and LH plasma levels in association with clinical rating and a secondary outcome was the epigenetic profile of HPA and HPG axis—coupled CpG sites with testosterone and LH levels.

Results: LH plasma levels were significantly higher in patients with hypersexual disorder than in healthy volunteers. No significant differences in plasma testosterone, follicle stimulating hormone, prolactin, and SHBG levels were found between the groups. There were no significant associations between DNA methylation of HPA and HPG axis—coupled genes and plasma testosterone or LH levels after multiple testing corrections.

Conclusions: Subtle dysregulation of the HPG axis, with increased LH plasma levels but no difference in testosterone levels may be present in hypersexual men. **Chatzittofis A, Boström AE, Öberg KG, et al. Normal Testosterone but Higher Luteinizing Hormone Plasma Levels in Men With Hypersexual Disorder. Sex Med 2020;8:243—250.**

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Key Words: Testosterone; Biological Psychiatry; Hypersexual Disorder; Epigenetics; HPG Axis

INTRODUCTION

Hypersexual disorder (HD) is conceptualized as a non-paraphilic sexual desire disorder with combined aspects of sexual desire dysregulation, sexual addiction, impulsivity, and compulsivity.[1] HD was originally suggested as a diagnosis but not included in the Diagnostic and Statistical Manual of Mental Disorders 5, mainly owing to concerns about the validity of the diagnosis.[2] Following studies supported high reliability and validity of the proposed criteria[3] and the criticism has been addressed.[4] Further suggesting the importance of the clinical diagnosis are the negative consequences for health with distress and impaired function for the individual,[1,5] and currently, compulsive sexual behavior disorder is included in the International Classification of Diseases-11 in the group of impulse control disorders.[6]

The regulation of sexual behavior is very complex including neuroendocrine systems, the limbic system and frontal lobe inhibitory effects.[7,8] Testosterone is implicated in sexual behaviour, but the explicit relationship is complex and different models are proposed to explain the effects of testosterone including cognition, emotions, autonomic responses, and motivation.[9] In general, low testosterone levels are related with a decrease in many of the body's sexual functions and have a bidirectional relationship with sexual behaviors that can in turn, alter the levels of sex hormones.[9,10] Most studies regarding testosterone and hypersexuality have been conducted on sexual offenders in forensic settings, and the reported higher testosterone levels may be related to antisocial traits and aggression rather than hypersexuality.[11] Despite the lack of knowledge regarding the gonadal activity on hypersexuality, it is a common praxis for more than 30 years to use antiandrogen therapy to target hypersexual symptoms in paraphilic patients and sexual offenders.[11,12] It is thus important to elucidate the relationship between hypersexuality and androgen activity, primarily concerning testosterone in non-criminal settings.

To our knowledge, there are hitherto no studies on gonadal influence in HD. The aim of this study was to assess testosterone and luteinizing hormone (LH) levels in men with HD compared with an age-matched control group of healthy men. A secondary aim was to investigate associations of the epigenetic profile of hypothalamus pituitary adrenal (HPA) and hypothalamus-pituitary-gonadal (HPG)—axis coupled CpG sites with testosterone and LH levels.

MATERIAL AND METHODS

Ethics

The study protocols were approved by the regional ethical review board in Stockholm (Dnr: 2013/1335-31/2), and the participants gave their written informed consent to the study.

Study Population

Patients

67 male patients with HD were recruited at the Center for Andrology and Sexual Medicine, through advertising in media and referrals to the Center. The patients were seeking medical and/or psychotherapeutic treatment that was provided after the examinations. The study population has been described previously in detail.[13] Inclusion criteria were a diagnosis of HD, available contact information, and the age of 18 years or older. The diagnosis was established using the Diagnostic and Statistical Manual of Mental Disorders-5—proposed criteria for HD, and participants needed 4 of 5 criteria to be included.[4]

The patient group used mainly pornography (54 patients), masturbation (49 patients), sex with consenting adults (26 patients), and cybersex (27 patients). The most common combination was masturbation and pornography (49 patients), meaning that everyone who used masturbation also used pornography. Moreover, 29 patients had 3 or more different sexual behaviors.

The diagnosis of HD and other psychiatric diagnosis were established by a trained psychiatrist and psychologist using the Mini International Neuropsychiatric Interview.[14] Patients with current psychotic illness, current alcohol or drug abuse, other psychiatric disorder that would require immediate treatment such as major depression with high suicidal risk, and serious physical illness such as severe hepatic or renal disease were excluded.

Healthy Volunteers

39 male healthy volunteers were recruited using Karolinska Trial Alliance (KTA) database. Karolinska Trial Alliance is a support unit founded by the Stockholm County Council and the Karolinska Institutet and functions as a Clinical Research Center at Karolinska University Hospital to facilitate clinical studies. The volunteers were included if they had the following: no serious physical illness, no previous or ongoing psychiatric illness, no first degree relative with either schizophrenia, bipolar disorder or completed suicide, and no previous exposure to serious trauma (natural disasters or assault). Healthy volunteers were evaluated with the same psychometric instruments as the hypersexual men. Individuals screened positive for pedophilic disorder were also excluded.

From the total of 40 healthy volunteers, one was excluded because of medical illness that was evident from laboratory results. An effort was made to age-match healthy volunteers to patients with HD and matching time of blood sampling to either the spring or fall was performed to minimize seasonal variations.

Assessments

All study participants were investigated with the following structured instruments:

The *Mini-International Neuropsychiatric Interview* (MINI 6.0) is a validated, structured diagnostic clinical interview for assessing psychopathology along the axis I.[14]

The *Hypersexual disorder screening inventory (HDSI)* with 7 items followed the criteria (5A and 2B criteria) of HD. Total

Table 1. Clinical characteristics of study participants (patients with hypersexual disorder and healthy volunteers)

Clinical characteristics	Patients N = 67	Healthy volunteers N = 39	Statistics (t-test, Kruskall-Wallis), P value
Age (years)			
Mean	39.2	37.5	P = .45
Range	19–65	21–62	
Std	11.5	11.9	
Diagnosis depression	n = 11, 16.4%	-	-
Diagnosis anxiety disorders	n = 12, 17.9%	-	-
Diagnosis other	n = 1, (ADHD)	-	-
Antidepressants	n = 11, 16.4%	-	-
HDSI			
Mean	19.6	1.6	P < .001
Range	6–28	0–9	
Std	5.7	2.2	
SCS			
Mean	27.8	11.1	P < .001
Range	12–39	10–14	
Std	6.9	1.2	
HD:CAS			
Mean	10.3	0.38	P < .001
Range	1–22	0–4	
Std	5.4	0.88	
MADRS			
Mean	18.9	2.4	P < .001
Range	1–50	0–12	
Std	9.7	2.9	
CTQ total (n = 65)			
Mean	39.95	32.53	P < .001
Range	25–80	25–70	
Std	11.48	8.75	

ADHD = attention deficit hyperactivity disorder; CTQ = childhood trauma questionnaire; HD:CAS = hypersexual disorder: current assessment scale; HDSI = hypersexual disorder screening inventory.

scores ranged from 0 to 28 with a minimum score of 3 needed on 4 of 5 A-criteria and 3 or 4 points on a minimum of 1 B-criteria, thus a minimum total score of 15 is needed for a diagnosis of HD.[3]

The *Sexual Compulsivity Scale (SCS)* includes 10 items regarding sexually compulsive behavior, sexual preoccupations, and sexually intrusive thoughts on a 4-point scale. It was developed for assessing high-risk sexual behaviours. Total scores ranged from 10 to 40, a score less than 18 indicates no sexually compulsivity, 18–23 indicates mild sexual compulsivity, 24–29 indicates moderate, and greater than or equal to 30 indicates high level of sexual compulsivity.[15]

The *Hypersexual Disorder: Current Assessment Scale (HD:CAS)* assessing the symptoms in the past 2 weeks before the clinical visit. The HD:CAS contains 7 questions with the first one (A1) asking for the type and the number of sexual behaviors reported. The following 6 questions (A2–A7) quantify these symptoms during the most recent 2-week time frame. Each question (A2–A7) is rated on a 5-point intensity scale (0–4) with total scores 0 to 24 points.

The *Montgomery-Åsberg Depression Rating Scale-Self rating (MADRS-S)* assessing the severity of depression.[16] The rating scale includes 9 questions on depressive symptoms, rated from 0 to 6 points with a total score from 0 to 54.

The *Childhood Trauma Questionnaire (CTQ)* for self-reported childhood trauma has 28 assessment items and 5 subscales measuring emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Each subscale gets scores between 5 and 25 (none to severe maltreatment).[17]

For details regarding the study participants, please see Table 1.

Blood Sample Collection and Analysis

All blood samples were taken in the morning approximately at 08.00 hours. Blood sampling for patients and healthy volunteers were performed equally between the spring and fall between the groups to minimize seasonal variations in sampling. A dexamethasone suppression test with dexamethasone 0.5 mg was performed with the results previously reported.[13] Total plasma testosterone, LH, and SHBG levels were analyzed by the electrochemiluminescence immunoassay COBAS (Roche, Basel, Switzerland) platform at the Department of Clinical Chemistry, Karolinska University Hospital, Huddinge. The testosterone
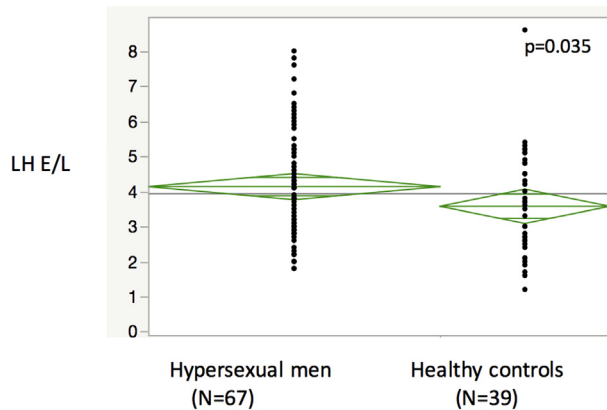
Figure 1. LH (luteinizing hormone) plasma levels in hypersexual men and healthy controls.

assay detection range was 0.087—52 nmol/L with intra-assay coefficients of variability (CVs) of 2.2% at 3.0 nmol/L and 2.0% at 18.8 nmol/L and interassay CVs of 4.7% at 3.0 nmol/L and 2.5% at 18.8 nmol/L. The LH assay detection range was 0.1—200 E/L with intra-assay CVs of 0.6% at 4.0 E/L and 0.6% at 26 E/L and interassay CVs of 1.5% at 4.0 E/L and 2.0% at 26 E/L. The SHBG assay detection range was 0.35—200 nmol/L with intra-assay CVs of 1.7% at 17 nmol/L and 2.2% at 42 nmol/L and interassay CVs of 0.3% at 17 nmol/L and 0.9% at 42 nmol/L. Follicle stimulating hormone (FSH) and prolactin were measured as per the standardized methods at the laboratory of Karolinska University (www.karolinska.se).

Epigenetic Analyses

Details about methylation profiling and data processing have been previously published.[18] For description of sample exclusion, CpG site annotation, and selection of HPA and HPG axis—coupled probes, please refer to Supplementary Material.

Statistical Analysis

All statistical analyses were performed using Statistical Package JMP 12.1.0 software (SAS Institute Inc, Cary, NC). Skewness and kurtosis of the distribution of continuous variables were evaluated by the Shapiro-Wilk test. LH levels were normally distributed both in patients with HD and healthy volunteers, whereas testosterone, SHBG, FSH, and prolactin plasma levels were not normally

distributed in healthy volunteers and patients, respectively. Unpaired Student t-test and Wilcoxon-Mann-Whitney test were subsequently used to investigate group differences in continuous variables between patients with HD and healthy volunteers. Correlational analyses were used to determine associations between the clinical and biologic variables as well as to check potential confounders. Tests of non-parametric or parametric correlations were performed using Spearman's rho or Pearson's r. All statistical tests were two-tailed. The P value for significance is <0.05.

Statistical analyses of the epigenetic sample were performed using R statistics (The R Foundation for Statistical Computing, Vienna, Austria), version 3.3.0. After the preprocessing steps, 87 samples remained to be included in the subsequent analysis of the 221 HPA and HPG axis—coupled CpG sites. The chi-squared test was used to detect differences in categorical variables, for example, gender, depression, and dexamethasone suppression test non-suppression status. For optimal covariates and association analysis of the epigenetic sample, please refer to Supplementary Material.

RESULTS

Testosterone, LH, FSH, Prolactin, and SHBG Plasma Levels in HD and Healthy Volunteers

Patients had significantly higher LH plasma levels than healthy volunteers, but there were no significant differences between plasma testosterone, FSH, prolactin, and SHBG levels in patients with HD compared with healthy volunteers, Figure 1, Table 2. Testosterone was significantly positively correlated with SHBG and LH (r = 0.56, P < .0001; r = 0.33, P = .0005) in all study participants. 11 patients were treated with antidepressants. There was no significant difference on LH plasma levels between patients taking and patients not taking medication (P = .7). Patients taking antidepressants had higher testosterone plasma levels than patients not treated with antidepressant (P = .04).

Clinical Ratings and Hormone Plasma Levels

The correlations between measures of hypersexuality (SCS and HD: CAS) and LH plasma levels were not significant. The correlations of testosterone plasma levels with measures of hypersexuality (SCS and HD: CAS) were not significant in the entire group (rho = 0.24, P = .06; r = 0.24, P = .05), Table 3.

Table 2. Testosterone, LH, FSH, prolactin, and SHBG plasma levels in patients with hypersexual disorder and healthy volunteers

Endocrine measurements	Patients (N = 67) Mean (SD)	Healthy volunteers (N = 39) Mean (SD)	Statistics (t-test, Wilcoxon-Mann-Whitney test), P value
Testosteron (nmol/L)	15.09 (4.49)	14.34 (4.29)	.313
SHBG (nmol/L)	32.59 (11.29)	35.15 (13.79)	.6
LH (E/L)	4.13 (1.57)	3.57 (1.47)	.035*
Prolactin (mIU/L)	173.67 (71.16)	185.21 (75.79)	.34
FSH (E/L)	4.12 (2.49)	4.24 (2.53)	.92

FSH = follicle stimulating hormone; LH = luteinizing hormone; SHBG, sex hormone—binding globulin.
A two-tailed P-value <.05 * was considered significant.

Table 3. Correlations (P values), (Spearman rho and Pearson's r) between testosterone and LH measures and clinical ratings in study participants

Endocrine measure	CTQ	MADRS-S	SCS	HD:CAS
Testosterone	0.0713 (0.5726)	−0.0855 (0.4916)	0.2354 (0.0551)*	0.24 (0.0505)*
LH	−0.1112 (0.3777)	0.1220 (0.3253)	−0.0078 (0.9501)	−0.17 (0.1638)
SHBG	−0.0179 (0.8877)	−0.1421 (0.2514)	0.1331 (0.2830)	−0.04 (0.7703)

CTQ = childhood trauma questionnaire; HD:CAS = hypersexual disorder: current assessment scale; LH = luteinizing hormone; MADRS-S = Montgomery-Åsberg depression rating scale-self rating; SCS = sexual compulsivity scale; SHBG = sex hormone−binding globulin. Italics mean Pearson r was used.
*$P < .1$.

Testosterone was significantly correlated with SCS in patients with HD (rho = 0.28, $P = .02$). There were no significant correlations between testosterone and LH plasma levels, depressive symptoms measured by MADRS or CTQ ratings, Table 3.

Investigation of Associations Between 221 HPA and HPG Axis−Coupled CpG Sites With Plasma Testosterone and LH Levels

No individual CpG site was significant after corrections were made for multiple testing using the false discovery rate method, for details, refer to Supplementary Material.

DISCUSSION

In this study, we found that male patients with HD had no significant difference in plasma testosterone levels compared with healthy volunteers. On the contrary, they had significantly higher plasma levels of LH. The mean testosterone and LH levels of both groups were within the reference range. To our knowledge, this is the first report of HPG dysregulation in men with HD. LH has a central role in the regulation of sexuality mainly through the consecutive production of androgens. Previous studies on LH plasma levels and sexual arousal have given contradictory results, which may be partly explained by more specific studies on LH pulsivity and bioactivity. Stoleru et al[19] reported that sexual arousal in young men has an effect on LH pulse signal resulting in postponing the second peak after the arousal and increasing its height.[19] It might also be that there are differences in the bioactive/immunoactive ratio of LH. Carosa et al[20] reported that patients with erectile dysfunction had a significantly lower bioactive/immunoactive ratio of LH than healthy men had, and this was reversed after the resumption of sexual activity.

Most studies on hormones and deviant sexual behaviors have been in forensic settings investigating sexual offenders. Kingston et al[21] reported that gonadotrophic hormones, FSH, and LH were positively correlated with hostility in the sex offenders and were better predictors for long-term recidivism than testosterone levels in a study following up sex offenders for up to 20 years. The authors argued that some sex offenders have a dysregulation of LH with a failure of downregulation independent of their testosterone levels. In addition, in a study comparing men with pedophilia and non-pedophilic paraphilia, as well as normal male controls, although there were no differences among groups in testosterone and LH levels after the infusion of 100 mcg of synthetic LH-releasing hormone, the pedophile group had more elevation of LH, compared with the other 2 groups.[22] It is, however, difficult to draw parallel between these findings reported in forensic settings and our study focusing on men with HD without pedophilia or history of sex offending.

The relationship between sexuality and testosterone levels is complex. Indeed, testosterone is directly related to sexuality and sexual arousal with effects on multiple systems including cognitive processes, emotions, autonomic processes, and motivation.[9,10] These effects can also be indirect through the conversion to estradiol and binding to respective receptors. Testosterone and LH levels are also affected by sexual behaviour and stimuli. Visual erotic stimulation, the frequency of orgasms through coitus or masturbation, and even anticipation of sexual interaction can influence testosterone levels.[9,10] Furthermore, the kind of stimuli, the context, and previous experiences can modulate these effects on testosterone levels. Rupp and Wallen[23], in a study of men exposed to visual erotica, argue that testosterone levels are modulated by experience, reporting that testosterone levels were more related to sexual interest in men viewing pornography who were repeatedly exposed to sexual stimuli and in men with more previous viewing experience of pornography before the study. The authors propose that testosterone is needed to enhance motivation and cognitive process when habituation of the stimuli has occurred through repeated exposure.[23] Although the testosterone levels did not differ between men with HD and healthy controls, the correlations between testosterone plasma levels and measures of hypersexuality showed a trend for significance in the entire group and a significant positive correlation in men with HD with highest testosterone levels in patients reporting more sexually compulsive behavior, sexual preoccupations, and sexually intrusive thoughts.

However, studies on testosterone in sex offenders reported mixed results, and a recent meta-analysis concluded that there is no support for difference in testosterone levels in sex offenders compared with non−sex offenders and that there might be differences within sex offenders as child molesters had lower testosterone.[24] But even regarding testosterone supplementation for sexual function, a systematic review of randomized

controlled trials by Huo et al[25] comes to the conclusion that, regarding libido, although there are more positive than negative studies, the results remain mixed. In addition, testosterone supplementation was not consistently effective in improving sexual function. Finally, most studies have been experimental, investigating the effects on testosterone and LH after the influence of an acute sexual stimulus, for example, sexual arousal film, masturbation, or coitus[19] and did not investigate the effects on the HPG axis in a more long-lasting condition such as in patients with HD. Thus, the finding of no difference of testosterone levels in hypersexual men compared with healthy volunteers is not surprising.

There are only a few studies investigating hypersexual men and endocrine systems. Safarinejad[26] measuring treatment effects of the long-acting analog of gonadotropin-releasing hormone, triptorelin, in non-paraphilic hypersexual men reported normal levels of baseline testosterone and LH levels, but the study design did not include a healthy control group. In that study, LH and testosterone levels as well as the sexual output (number of sexual attempts) of the hypersexual men decreased with treatment showing the close relationship of hormone levels and sexuality.

Testosterone levels have also been related to anxiety and depressive symptoms in hypogonadal men.[9,10] We did not find significant correlation between testosterone levels and depressive symptoms. HD includes in its definition that the behavior can be a result of dysphoric states and stress,[1] and we have previously reported a dysregulation with hyperactivity of the HPA axis[13] as well as related epigenetic changes in men with HD.[18]

There are complex interactions between HPA and HPG axis, both excitatory as well as inhibitory with differences depending on the developmental stage of the brain.[27] Stressful events through effects of the HPA axis may cause an inhibition of LH suppression and consequently of reproduction.[27] The 2 systems have reciprocal interactions, and early stressors may alter neuroendocrine responses through epigenetic modifications.[28–30]

The correlations of testosterone plasma levels with measures of hypersexuality (SCS and HD: CAS) were at a trend level in the whole group, and testosterone was significantly positively correlated with SCS in patients with HD. The SCS measures sexually compulsive behavior, sexual preoccupations, and sexually intrusive thoughts and was developed for assessing high-risk sexual behaviors.[15] Sexual risk takers' behaviors include frequent sex with different partners, increased number of sexual partners, unprotected sexual intercourse, unprotected anal intercourse, acquired sexually transmitted diseases, and use of drugs and alcohol before sex.[1,31] Testosterone is implicated in risk taking behaviors and together with cortisol, as per the dual hormone hypothesis, they modulate risk taking.[32] This dual hormone hypothesis proposes that status-relevant behaviors such as aggression and dominance are positively related with testosterone only when the levels of cortisol are low but not when cortisol

levels are high. In this line, we have recently reported that the CSF testosterone/cortisol ratio was significantly positively correlated with impulsivity and aggressiveness in a cohort of suicide attempters.[33] Furthermore, cortisol plasma levels was negatively correlated with SCS scores in men with HD.[13] Thus, both the negative correlation of cortisol levels with SCS and the positive correlation of testosterone levels with SCS are in line with the dual hormone hypothesis. Sexual desire is also multifaceted, and contextual factors such as stress, gender, and desire target might moderate associations with hormones such as testosterone.[34,35] The proposed mechanisms might include the HPA and HPG interaction, the reward neural network, or the inhibition of regulation impulse control of prefrontal cortex regions.[32]

An alternative explanation would be that of the compensatory hypogonadism, which usually presents with normal or in the lower limits, testosterone plasma levels, and higher or in the higher limits of LH plasma levels as a compensatory mechanism. However, compensatory hypogonadism is related to advancing age and chronic comorbidities, unlike our sample, which is age matched to the control group and relatively free from other comorbidities.

Regarding the epigenomics, genome-wide methylation chips with more than 850 K CpG sites were used, but we focused on candidate genes related to HPA axis based on our previous findings[18] as well as common HPG axis—related genes and novel reported systems related to sexual behavior such as oxytocin and kisspeptin.[36–38]

In the multiple linear regression models for plasma testosterone levels, 12 CpG sites were nominally significant and 20 CpG sites for plasma LH levels. No individual CpG site was significant after corrections for multiple testing. This is the first epigenetic study of HPG axis—associated genes in HD, and we have previously reported epigenetic changes in HPA axis—associated genes.[18] Negative results should be interpreted with caution. Owing to the small sample size, it would be difficult to detect small effect sizes, especially after corrections for multiple testing.

The strengths of the study are a carefully selected, homogenous population of hypersexual men, the presence of an age-matched control group of healthy volunteers, excluding history of or present psychiatric disorders, family history of major psychiatric disorders, and severe traumatic experiences. Furthermore, the accounting for possible confounders in the analysis such as childhood adversity, depression, neuroinflammatory markers, and dexamethasone test results. Limitations such as the self-reporting of childhood adversity and the relatively small sample for the epigenetic analysis have to be mentioned. An additional strength is methylation patterns are highly tissue dependent, and the negative epigenetic findings could be related to the tissue source (whole blood). In addition, recent sexual activity might be a possible confounder by maintaining hormone levels[39] as we did not control for

latest sexual activity. However, there was no association between hormone levels and sexual activity, in the past 2 weeks, measured with HD:CAS that would indicate such an effect. Furthermore, testosterone was measured by an immunoassay rather than the more accurate liquid chromatography—mass spectrometry methods.

Finally, the cross-sectional design of the study is a limitation for casual conclusions, and there is a need for replication in an independent cohort as this is the first study of HPG axis and epigenetics in HD.

In conclusion, we report for the first time increased LH plasma levels in hypersexual men compared with healthy volunteers. These preliminary findings contribute to growing literature on the involvement of neuroendocrine systems and dysregulation in HD.

Directions for further research in HD can be seen in different aspects. Most of the research has been conducted in men and in biased populations such as sex offenders. Thus, clinical phenotypes of hypersexual women, gender differences, and clinical populations are lacking. Comorbidities, especially with other psychiatric disorder including substance and behavior addictions needs to be clarified. One approach could be to study patients with HD/compulsive sexual behavior disorder without comorbidities. Finally, it would also be of great interest to apply the research domain criteria framework. Neuroimaging, molecular, genetic, as well as epigenetic studies in combination with traits such as aggression, impulsivity, and antisocial behavior would elucidate the pathophysiology of the disorder.

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STATEMENT OF AUTHORSHIP

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.esxm.2020.02.005.