CLINICAL INVESTIGATION

Hair cortisol and chronic stress exposure in chronic Hepatitis B patients

Hie-Won Hann[1], Jerrold Meyer[2], Grace Park[1], Peter D Block[3], Hee-Soon Juon[4]*

[1]Liver Disease Prevention Center, Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA
[2]Department of Psychological, Brain Sciences, University of Massachusetts, Amherst, Massachusetts, MA 01002, USA
[3]Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA
[4]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, PA 19107, USA

*Author for correspondence: hee-soon.juon@jefferson.edu

Abstract

Background: The purpose of this study is to address the prolonged exposure to stress associated with chronic HBV infection. We, therefore, explored the measure of stress cortisol hormone (CORT) in the hair as a biomarker of chronic stress in CHB patients.

Materials and Methods: Eligible CHB patients identified from an existing patient cohort were enrolled in this prospective study. Data collection was done using medical chart reviews, face-to-face interview in Korean or English, and hair and blood samples.

Results: We collected hair samples of 50 CHB patients (age 34-74 years) with the duration of CHB diagnosis (1-51 years, 23.8 ± 10). About three-fourths were male. More than 40% had family history of HBV infection. Hair samples weighing 19.6-29.9 mg were processed and analyzed for cortisol. Mean cortisol levels were 16.42 pg/mg (27.59 SD) ranging from 2.7 to 168.1 pg/mg. About 16% (n=8) had below normal hair cortisol level (<5.9 pg/mg). Two patients had high above normal hair cortisol levels (112.2 and 168.1 pg/mg). The rate of distress measured by Distress Thermometer (DT) (defined by the DT cutoff >=4) was 48%. Distress was positively correlated with hair cortisol level (r=.395, p<.05) among those with below-normal hair cortisol levels.

Conclusion: The mean of hair CORT in our CHB patients (16.4, 95% CI: 8.5-24.4) was lower than other studies of adults, suggesting long-term suppression of hair cortisol production in the course of CHB and antiviral therapy. This study indicates a possible hypothesis that the cortisol levels of CHB patients might have been suppressed and their HPA-axis down-regulated after having been stressed for years related to the disease. This study suggests a need for further research to determine the longitudinal effects of chronic stress on hair cortisol levels and liver disease progression in CHB patients.

Keywords: hair cortisol • chronic stress • self-reported distress • duration of disease • Asian Americans • hepatitis B

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Introduction

The hepatitis B virus (HBV) is a blood-borne pathogen that establishes infection within the liver [1,2]. An estimated 2 billion individuals worldwide have been infected and over 350 million people have developed chronic hepatitis B (CHB) [3]. Without treatment, CHB significantly heightens patients' risk for future hepatic complications, including cirrhosis and hepatocellular carcinoma [3]. HBV is known to exert suppressive effects on the host innate [4,5] and adaptive immune responses [6,7], thus maintaining persistent infection in the host.

Host factors that contribute to liver disease progression in CHB remain incompletely understood [8]. Increasing evidence suggests that psychosocial stress has adverse effects on a variety of medical conditions, including chronic liver disease [9]. However, a paucity of research has examined the effects of chronic stress on CHB [10-12], despite upwards of 90% of patients with HBV considering their diagnosis a significant life stressor [13-15].

The hormonal responses of the Hypothalamic-Pituitary-Adrenal (HPA) axis were emphasized in Hans Selye's (1956, 1974) research on a nonspecific physiological reaction that occurs in response to excessive stimulation [16,17]. Cortisol is a glucocorticoid hormone released by the adrenal cortex through stimulation of HPA axis. Cortisol is commonly known as a stress hormone because it is released in higher doses under stressful conditions. While the measurement of cortisol from blood, saliva, urine (i.e., 24 to 36 hours) provides valuable information about cortisol dynamics and stress reactivity, cortisol levels in hair have become a novel and well-appreciated technique to determine long-term (i.e., months to year) total cortisol exposure [18]. First developed in 2004 [19], extraction of the stress hormone cortisol (CORT) in the hair has become a commonly examined biomarker of the stress response due to the ease and non-invasiveness of collection [20]. Successful application of CORT has been applied to studies of patients with Cushing's Disease [21,22], psychiatric symptoms and disorders such as depression and Post-Traumatic Stress Disease (PTSD) [18,23], and other situations associated with elevated risk of chronic stress (e.g., endurance athletes, shiftwork, unemployment, chronic pain, stress in neonates, and pregnancy) [24-28].

Accumulating evidence has clarified the relationship between stress and cortisol levels. While acute stress through the HPA-axis initially leads to hyperactive functioning prolonged stress exposure can overwhelm coping mechanisms leading to a state of exhaustion and hypoactive functioning. In turn, both hyper- and hypocortisolism are associated with stress-related disease [29]. Hypercortisolism is associated with a number of various diseases including cardiovascular disease, type-2 diabetes, and depression [30-32]. Conversely, hypocortisolism has been reported in patients with a variety of stress-related disorders, including chronic fatigue syndrome, fibromyalgia, lower back pain, post-traumatic stress disorder (PTSD), and burnout [29,33-35]. Importantly, no study has attempted to measure chronic stress among CHB patients through hair CORT.

To investigate the association of prolonged exposure to stress with CHB, we quantified the level of hair CORT in CHB patients from clinic-based cohort data and correlated with subjective stress (e.g., self-reported) from the same clinic-based patient cohort. To the best of our knowledge, this is the first study to measure hair CORT in CHB patients.

Materials and Methods

Study population

The subjects in this study were identified from an existing clinic-based patient cohort. The cohort was comprised of patients who visited the Liver Disease Prevention Center (LDPC), Division of Gastroenterology and Hepatology at Thomas Jefferson University Hospital. Among the patients visiting LDPC, 50 patients were recruited. The 50 patients recruited met all of the following criteria: 1) Patients older than 18 years, 2) Patients with CHB with positive HBsAg for more than 6 months, and 3) Patients able to provide informed consent for the participation. Patients with other viral infections with HCV, HIV or other viruses were excluded.

Data collection procedures

Patients who met the eligibility criteria were invited to participate in the study. After the written consent form was obtained, a total of 50 CHB patients were interviewed in Korean or English to collect information about sociodemographic, disease duration, family history of HBV infection, Thermometer Distress, stressful life events, social supports, and mental and physical health. Clinical data were obtained from medical chart review and consultation with the provider. Hair samples were cut from the posterior vertex of the scalp, as close to the scalp as possible. The proximal 3 cm of the hair strands were used, corresponding to the growth of hair roughly to a period of 3 months. The collected hair samples were stored in an aluminum foil pouch per each sample to avoid contamination. Then, the collected samples were sent to University of Massachusetts's Dr. Jerrold Meyer's lab for the extraction, grinding, and analysis of the CORT [36]. Each participant was given $20 gift card for the appreciation of participation. The protocol was approved by the Institutional Review Board at Sidney Kimmel Cancer Center, Thomas Jefferson University.

Measures

Hair CORT: As this study focused on the level of hair CORT, we included 50 CHB patients. One patient did not have any detectable hair CORT since he was taking corticosteroid medication after a kidney transplant and was excluded from the data analyses, leaving a final analyzed sample of 49 CHB patients. As hair CORT was not normally distributed (Kolmogorov-Smirnov test: p<0.01), hair CORT was logarithmically transformed to attain normal distribution and used in the data analyses. At present, there are no normative value ranges established to hair CORT [37]. For illustrative purpose in Table 1, the cortisol values were divided into three groups: 1) low (<5.9 pg/mg); 2) intermediate (5.9-22.6 pg/mg); and 3) high (>22.6 pg/mg) [38].

Table 1. Descriptive statistics of distress thermometer and hair CORT (n=49)

	n	%
Hair CORT (pg/mg) mean ± SD (range)	16.42 ± 27.59 (2.7-168.1)	
Log hair CORT (pg/mg) mean ± SD (range)	2.35 ± 0.77 (0.99-5.12)	
2.7-5.4 (low)	8	16.3
5.9-17.5 (intermediate)	36	73.5
26.1-168.1 (high)	5	10.2
Distress Thermometer		
0-3	26	52
4-10	24	48

Distress: The Distress Thermometer (DT) is a global screener of distress that consists of a one-item, 11-point Likert scale represented visually as a thermometer with markings from 0 (no distress) to 10 (extreme distress). Validity has been established in comparison to other well-known distress measures [39]. A cut-off score of 3 designated low distress versus 4 to 10 indicating moderate to severe distress.

Demographic variables: were collected from medical chart review and questionnaire administered during the date of the interview. These variables include age, gender, disease duration, family history of HBV infection, liver cirrhosis and liver cancer, alcohol and tobacco use, and compliance with antiviral therapy.

Statistical analysis

We conducted Kolmogorov-Smirnov tests to determine the normality of hair CORT. The measured cortisol values were log transformation due to skewness in the distribution. Means presented in Table 2 are based on both raw values and transformed values. We examined the correlations between self-reported distress and log-transformed hair CORT using Spearman correlations. All statistical analyses were performed using STATA 14.

Table 2. Characteristics of the study population (n=50)

	Value	N (%)
Age	Mean ± SD (range)	55.34 ± 10.02 (34-74)
Gender	Male	37 (74%)
	Female	13 (26%)
Education Level	<High School	3 (6%)
	High School+	16 (32%)
	College+	31 (62%)
Country of Birth	South Korea	46 (92%)
	China	3 (6%)
	Kazakhstan	1 (2%)
Having Health Insurance	Yes	48 (96%)
	No	2 (4%)
Smoking Status	Never	29 (58%)
	Former	12 (24%)
	Current	9 (18%)
Drinking Status	Never	25 (50%)
	Current	25 (50%)
Family history of HBV infection	Yes	21 (42%)
	No	28 (56%)
	Not Sure	1 (2%)
Duration of HBV diagnosis	Mean ± SD (range)	23.8 ± 10 (1-51)
Distress	Mean ± SD (range)	5.38 ± 2.39 (1-10)

Results

Characteristics of the study population

The characteristics of the 50 patients are shown in Table 2. The participant average age was 55.43 years (range 34-74, SD 10.02). About three-fourths were male. About two-thirds had more than college education. 47 were Korean (94%) and 3 were Chinese descent (6%). Also, 46 were born in South Korea (92%), 3 were born in China (6%) and 1 was born in Kazakhstan (2%). Most had health insurance (96%). More than 40% had family history of HBV infection (Table 2).

Distribution of hair CORT

Of 49 patients, hair samples weighing 21-195 mg were processed and analyzed for cortisol [36]. Intra- and inter-assay coefficients of variation were <10 percent. Values were converted into pg/mg hair for data analysis and presentation. Mean cortisol levels were 16.42 pg/mg (27.59SD) with a median concentration of 10, ranging from 2.7 to 168.1. Table 1 also shows the log-transformed hair CORT (2.35 ± 0.77, range of 0.99 to 5.12).

Based on very skewed distribution to lower end and 3 outliers (≥ 1.74), hair CORT was also categorized into three (low, intermediate, and high CORT): 16% had low CORT (2.7-5.4 pg/mg), 74% had intermediate CORT (5.9-17.5 pg/mg), and 10% had high CORT (26.1-168.1 pg/mg). As shown in Table 1, about half of CHB patients had moderate to severe distress measured by DT (Figure 1).

Relationships between the distress and hair CORT

Figure 1 shows the scatter plots of DT and hair CORT. A Spearman correlation coefficient and associated p-value were calculated. Distress and CORT were not related in total (rho=0.01,p=0.991). When stratified by hair CORT (low, intermediate, high), the relationship between DT and CORT was different. Among those with a low level of CORT, the higher the scores of DT, the higher the level of CORT (rho=0.71,p<0.05). On the other hand, there were no significant associations between DT and hair

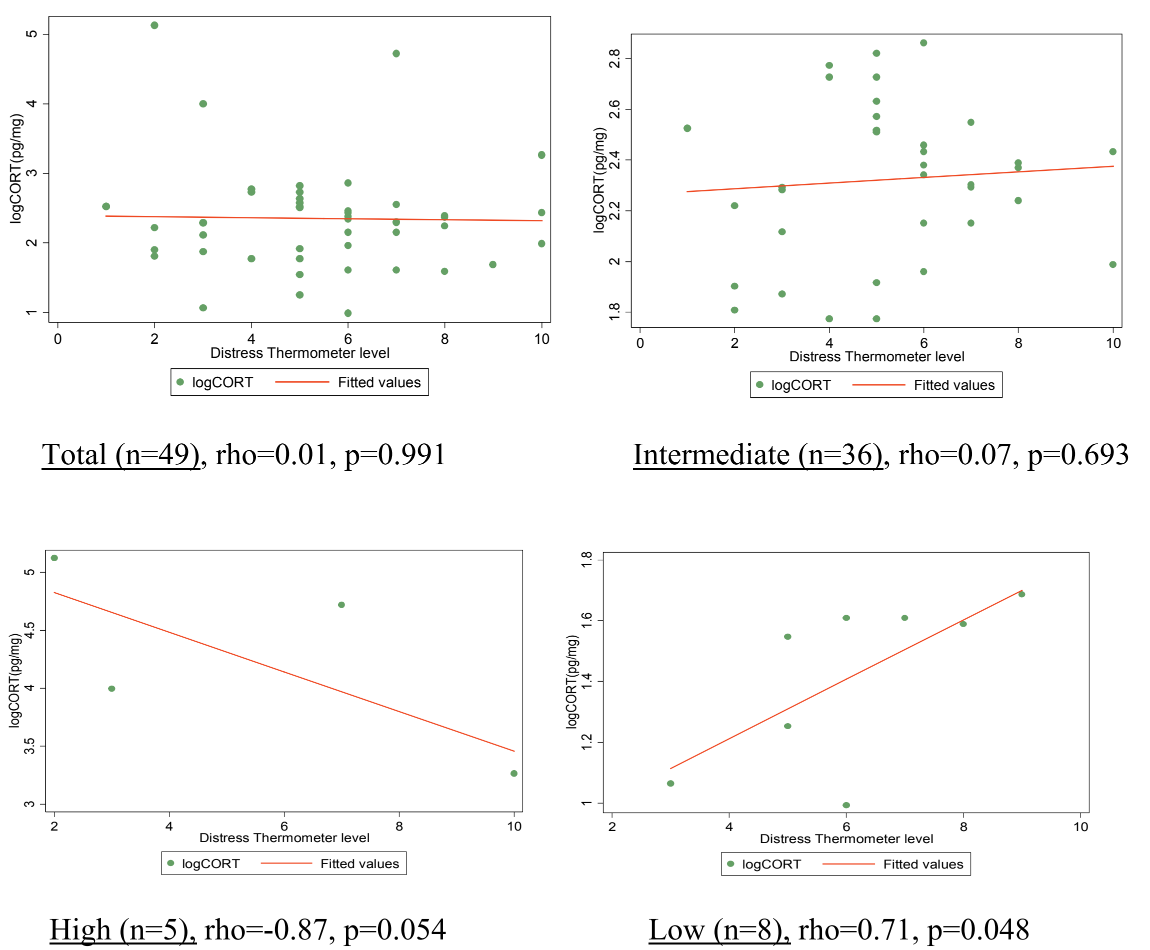

Figure 1: Relationship between distress and hair CORT.

CORT for those with intermediate and high cortisol levels.

Discussion

The mean of hair CORT in our CHB patients (16.4, 95% CI: 8.5-24.4) was lower than other studies of adults over 50 years of age whose mean of hair CORT ranged from 21.0 to 40.5 pg/mg [40-42]. It suggests long-term suppression of hair cortisol production in the course of HBV infection and antiviral therapy. Low hair CORT might indicate a specific pathogenic mechanism with cortisol production. This may explain the low cortisol levels observed in our CHB patients who are allegedly under chronic stress while suffering from CHB for years, most of them infected with HBV since birth. The rate of cortisol metabolism is decreased in liver disease [43]. In patients with liver disease, the physiologic action of cortisol is prolonged followed by depression of cortisol synthesis and secretion [43]. On the other hand, the association between childhood trauma and low hair cortisol level in depressed patients and health control subjects [44]. Similar findings were observed in patients who are under long-term stress show a down-regulation of their HPA-axis [45].

We found no association between distress and hair CORT in total. However, we found the positive association between distress and hair CORT among those with a low level of CORT: the higher scores of DT, the higher level of CORT. Nevertheless, we are careful about this association due to small sample size. Additional work needs to be done to explore this relationship in a large study sample.

Our study suggests a need for further research to determine the longitudinal effects of stress on hair cortisol levels and liver disease progression in patients with CHB. This group of patients belonged to those who have stated being stressed for years related to the disease.

Limitations of this study include being a single institutional study, as well as utilizing a predominately highly educated and health-insured patient population. In turn, extrapolation of our findings to the general CHB population is limited, warranting expanded investigations into the relationship of stress and CHB via hair CORT analysis.

Conclusion

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Conflicts of Interest

Hie-Won Hann receives clinical research grants from Gilead, Assembly Biosciences and Trio-Health and serves the Advisory Board of Gilead Sciences.

None for all other authors.

Executive summary

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