Psychometric Profiles and Hypothalamic-Pituitary-Adrenal Axis Function in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Purpose: Abnormal regulation of the hypothalamic-pituitary-adrenal axis and diurnal cortisol rhythms are associated with several pain and chronic inflammatory conditions. Chronic stress may have a role in the disorder of chronic prostatitis/chronic pelvic pain syndrome related to initiation or exacerbation of the syndrome. We tested the hypothesis that men with chronic pelvic pain syndrome have associated disturbances in psychosocial profiles and hypothalamic-pituitary-adrenal axis function.

Materials and Methods: A total of 45 men with chronic pelvic pain syndrome and 20 age matched, asymptomatic controls completed psychometric self-report questionnaires including the Type A personality test, Perceived Stress Scale, Beck Anxiety Inventory and Brief Symptom Inventory for distress from physical symptoms. Saliva samples were collected on 2 consecutive days at 9 specific times with strict reference to time of morning awakening for evaluation of free cortisol, reflecting secretory activity of the hypothalamic-pituitary-adrenal axis. We quantified cortisol variations as the 2-day average slope of the awakening cortisol response and the subsequent diurnal levels.

Results: Men with chronic pelvic pain syndrome had more perceived stress and anxiety than controls ($p < 0.001$). Brief Symptom Index scores were significantly increased in all scales (somatization, obsessive/compulsive behavior, depression, anxiety, hostility, interpersonal sensitivity, phobic anxiety, paranoid ideation, psychoticism) for chronic pelvic pain syndrome, and Global Severity Index rank for chronic pelvic pain syndrome was 93rd vs 48th percentile for controls ($p < 0.0001$). Men with chronic pelvic pain syndrome had significantly increased awakening cortisol responses, mean slope of 0.85 vs 0.59 for controls ($p < 0.05$).

Conclusions: Men with chronic pelvic pain syndrome scored exceedingly high on all psychosocial variables and showed evidence of dysfunctional hypothalamic-pituitary-adrenal axis function reflected in augmented awakening cortisol responses. Observations suggest variables in biopsychosocial interaction that suggest opportunities for neurophysiological study of relationships of stress and chronic pelvic pain syndrome.

Key Words: prostatitis, pelvic pain, stress, hydrocortisone

In most people the diurnal rhythm of the cortisol cycle is marked by 2 main characteristics: 1) a peak awakening cortisol response within 30 minutes after awakening in the morning; and 2) a gradually decreasing slope throughout the day, reaching the lowest levels late in the evening. These endocrine patterns are consistent, show high intraindividual stability across time and appear to be markers for subtle changes in HPA axis regulation.[1]

Stress triggers a cascade of pathophysiological events that involve activation of 2 pathways: the HPA axis and the autonomic nervous system. Chronic activation of the physiological stress response induces putative glucocorticoid resistance and altered immunity, release of proinflammatory cytokines and prostaglandins that may contribute to pain syndromes and, ultimately, to cycling psychological distress. Clinicians have anecdotally observed that stress exacerbates symptoms of prostatitis,[2] and chronic stress experiments in rats can specifically induce histological inflammation in the prostate.[3] Genetic factors and psychological variables, eg personality traits, modulate reactivity and vulnerability to stress.[4–6] Evidence from our case studies shows that manual physiotherapy with myofascial trigger point release and paradoxical relaxation therapy, both physical and cognitive behavioral therapy, can provide pain relief in some patients with CPPS.[7] Once it is understood how stress induced neurobiochemical changes may relate to pelvic pain in men, we may modulate these effects, and develop new and innovative approaches for the prevention and treatment of CPPS. Despite the likely relevance of stress related neurohormones in the disease process of CPPS, these factors have not been systematically evaluated. In this study we tested the hypothesis that CPPS is associated with psychological dysfunction as well as endocrine dysregulation of the HPA axis.

PATIENTS AND METHODS

Patients

Men referred to the Stanford University Hospital Urology Clinic from October 2005 to May 2007 with symptoms of

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CPPS (NIH category IIIA and IIIB) for at least 3 months within the last 6 months were invited to participate in the study. Participants were required to be 18 years of age or older, have a NIH-CPSI total score of 12 or greater (scale of 0 to 43), and a nonzero pain score at of enrollment. Approximately 90% of men with CPPS who met the entry criteria agreed to participate in the study. Healthy men with no history or evidence of GU disease or chronic pain conditions were recruited as controls by newspaper advertisement from the same socioeconomic community and prospectively age matched to the CPPS cohort. No analgesics, psychotropic drugs or systemic corticosteroids were allowed for at least 2 weeks before study entry. The protocol was reviewed and approved by the internal review board. Subjects received monetary compensation for participation.

Symptom Assessments

The NIH-CPSI questionnaire was used to quantify pelvic pain and urinary symptoms at the screening visit and immediately before the diurnal cortisol study.

Psychometric Assessments

Baseline psychological and psychosocial stress self-reported questionnaires were answered in the home setting. We measured psychological distress with the BSI of the SCL-90R, a 53-item inventory that scores 9 symptom dimensions: depression, anxiety, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, phobic activity, paranoid ideation, psychoticism (social alienation), and the GSI, an overall measure of distress.[8] The BSI surveys patient problems and how bothersome during the past 7 days. Responses are a 5-point Likert scale of 0 (not at all) to 4 (extremely bothersome). Raw scores convert to normalized T scores with equivalents based on adult male, nonpatient (nonpsychiatric) profiles from a reference population. The T scores are matched with percentile ranks for comparison with published norms. The BSI has well established norms, reliability and validity.

The Bortner Type A Personality Test categorized personality based on response to stress. Scores between 85 and 154 denote a Type A behavior pattern. The Beck Anxiety Inventory, a 21-item inventory, assessed symptoms of anxiety which are minimally shared with depression. Scores range from 0 to 63.

The Perceived Stress Scale, a 14-item questionnaire, measured perception of stress, feelings and thoughts during the past month. The PSS assesses the degree to which subjects perceive their lives as unpredictable, uncontrollable and with burden overload and includes direct inquiries about current levels of experienced stress. Scores range from 0 to 40.

Procedures for Salivary Cortisol Collection and Assessment

The measurement of cortisol in salivary samples accurately reflects levels of physiologically active unbound (free) cortisol in the blood, which diffuses from the blood to saliva. Cortisol secretion correlates with serum ACTH with an approximate 15 minutes delay and is considered to accurately reflect secretory activity of the HPA axis.[9] Patients collected saliva on 2 consecutive days at 9 points with strict reference to time of morning awakening: immediately upon waking, at 15-minute intervals for the next hour, and then an additional 4 samples at 3-hour intervals throughout the day. Awakening was either spontaneous or by alarm clock. To assure compliance with the collection procedures, the participants were given an electronic watch that beeps at designated times for saliva collection. Because cortisol levels vary during the day subjects were informed it was essential to collect samples at the designated time intervals and to enter collection times on a daily log. Subjects collected saliva in sterile Salivette tubes (Sarsted Inc., Newton, North Carolina) with small cotton swabs in capped plastic vials. This noninvasive technique was used for at-home or work based collections to interfere minimally with normal daily routines. Participants were instructed to refrain from eating, drinking, chewing gum, smoking, brushing teeth or using mouthwash for 30 minutes before collections and to refrigerate samples immediately or place them in an insulated cold bag until refrigeration for return to the clinic.

Saliva samples were stored at −70C before laboratory centrifugation and assayed for salivary cortisol by luminescence immunoassay with reagents provided by Immuno-Biological Laboratories, Inc., Hamburg, Germany. Samples from each subject were assayed in duplicate in the same batch by the Stanford GCRC laboratory. Assay sensitivity was 0.015 μg/dl. Intra-assay variation on low, medium and high controls averaged 15.5%, 10.2% and 7.6%, respectively. The mean values of the low, medium and high controls were 0.077, 0.24 and 0.93 μg/dl, respectively. The inter-assay coefficients of variation for the low, medium and high controls were 9.8%, 8.8% and 6.6%, respectively.

Data Analyses

We used SPSS® software for all statistical tests. We examined differences in psychosocial measures, medical variables and salivary cortisol with the Mann-Whitney U test (2-tailed) and Student's t test, and demographics with multivariate logistic regression and chi-square analysis. Salivary cortisol data were log transformed to stabilize the variance. Although we log-transformed cortisol values for all statistical analyses, the means and SD/SEM of untransformed values are presented. Diurnal or daytime cortisol slope was calculated by regressing cortisol values at time of awakening as the baseline, the 60 minutes and all subsequent time points for 2 days. Waking cortisol rise was the 2-day average of the difference between the cortisol levels at waking plus 30 minutes. Correlations were determined with the Spearman rank test. For all analyses, significance was at $\alpha = 5\%$.

RESULTS

A total of 65 subjects, 45 men with CPPS and 20 controls were enrolled in the study; all participants completed questionnaires and collected salivary samples as requested. Demographic characteristics are presented in table 1. Subjects in both groups were successfully age matched ($p = 0.82$) and 60% to 70% were white. They were highly educated, as approximately 70% had college or graduate/professional degrees. The groups showed no differences in distribution based on demographic variables (all $p > 0.05$). CPPS patients had a mean NIH-CPSI total score of 25 (± 6.7) and a median symptom duration of 39 months.

The 2 groups were discriminate on psychological variables. Patients with CPPS had significantly more perceived