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Sexual well-being and diurnal cortisol after prostate cancer treatment

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Abstract

Sexual dysfunction and psychological distress are common after prostate cancer. Research has not examined the role of neuroendocrine markers of stress (e.g. cortisol). This study examines whether sexual functioning or sexual bother is associated with diurnal cortisol. Men treated for prostate cancer completed the University of California–Los Angeles Prostate Cancer Index and provided saliva samples four times daily for cortisol assessment. Higher sexual bother, but not sexual functioning, was associated with steeper cortisol slope. Better sexual functioning, and not sexual bother, was significantly associated with the cortisol awakening response. Assessment of stress and stress-reducing interventions might be warranted in sexual rehabilitation after prostate cancer.

Keywords

cortisol, hypothalamic–pituitary–adrenal axis, prostate cancer, sexual bother, sexual functioning

Introduction

Prostate cancer (PC) and its treatment affect patients' quality of life across biological, psychological, and social domains including sexual health (Chung and Brock, 2013). Changes in sexual functioning such as altered libido and erectile dysfunction are common consequences of treatment (Sanda et al., 2008). In addition to functionality, sexual bother or psychological distress related to sexual problems can also occur after PC treatment and might be associated with relational disruption with intimate partners. With early-stage disease, greater sexual dysfunction, younger age, and using erectile aids are associated with higher sexual bother (Gacci et al., 2009). Resultantly, sexual dysfunction and related psychological distress constitute daily and chronic stress that interferes with adjustment across the PC continuum.

The hypothalamic–pituitary–adrenal (HPA) axis is a primary system involved in the physiological response to stress and is stimulated by physical or psychological stressors like those

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endured with sexual dysfunction. Activation of the HPA axis signals a cascade of hormones including glucocorticoids such as cortisol, which exert immunosuppressive effects, regulate metabolic processes, and provide negative feedback to rapidly resume physiological homeostasis (Gaffey et al., 2016). In healthy adults, cortisol peaks 30–45 minutes after morning waking and reaches a nadir in the evening (Clow et al., 2010). Altered cortisol patterns (e.g. elevated afternoon cortisol), which are signatures of HPA axis dysregulation, have been observed in PC patients who report more stress, higher depressive symptoms, and lower quality of life (Hoyt et al., 2016; Hsiao et al., 2011; Sharpley et al., 2016). Despite the significant impact and chronicity of sexual problems after treatment, biobehavioral mechanisms (e.g. neuroendocrine stress dynamics) underlying impaired sexual function and distress are not well delineated. That is, if physiological stress responses are associated with sexual quality of life after PC, are such responses underlying both functional and emotional domains?

In non-cancer samples, men with erectile dysfunction display elevated levels of cortisol, norepinephrine, and inflammatory markers (including interleukin (IL)-6 and C-reactive protein (CRP)), as well as testosterone deficiencies. Dysregulation in cortisol rhythm might further inhibit male sexual arousal (Granata et al., 1995; Guigliano et al., 2004; Kobori et al., 2009; Sansone et al., 2014; Uckert et al., 2003). Elucidating biobehavioral mechanisms that distinguish PC patients' sexual dysfunction and sexual bother will help reveal the etiology of men's sexual quality of life and guide recommendations for stress regulation.

The aim of this study was to determine whether sexual functioning or sexual bother is associated with diurnal cortisol. It was hypothesized that poorer sexual functioning and greater sexual bother would be associated with indices of cortisol dysregulation (both function and bother), including a flatter diurnal slope, lower diurnal output, and lower morning cortisol rise.

Methods

Participants

A total of 66 men (M age = 65.8 years; standard deviation (SD) = 9.0) who underwent radical prostatectomy or radiation therapy for localized PC within the prior 2 years were recruited via physician/clinic referrals, community outreach, and institutional tumor registry. Participants were excluded for medical comorbidities (e.g. active infection) or medications (e.g. steroids) that could confound cortisol evaluation; those with severe mental illness or regular smokers were also excluded.

All procedures were approved by the University of California–Los Angeles (UCLA) Institutional Review Board.

Measures

Sexual functioning and bother. The University of California–Los Angeles Prostate Cancer Index (UCLA-PCI) is a self-report measure of sexual functioning and sexual bother over the past 4 weeks (Litwin et al., 1998). The UCLA-PCI is a 20-item disease-specific questionnaire with strong psychometric properties. Each domain is scored from 0 to 100; higher scores correspond with better functioning. This study used standard scoring procedures, including the single sexual bother item (i.e. Overall, how big a problem has your sexual function been for you?) and the sexual functioning subscale (Cronbach's alpha = .91). The sexual functioning subscale includes questions about sexual desire, engagement in sexual activity, ability to reach orgasm, and erection quality and frequency.

Negative affect. The Positive and Negative Affect Schedule (PANAS) was used to assess negative affect. The scale includes 10 items measuring negative affective states experienced during the past few weeks (Watson et al., 1988; $\alpha = .92$).

Diurnal cortisol was assessed with saliva samples collected at home using Salivette collection tubes (Sarstedt, Inc., Nümbrecht, Germany). Participants collected saliva upon awakening (morning), 30 minutes post-awakening, 8 hours

post-awakening (afternoon), and at bedtime on three consecutive days. They were instructed not to eat, drink, or brush teeth 20 minutes before sampling. Participants self-reported compliance via use of a call-in line at the time of each collection and daily compliance log. Salivettes were stored in a −20°C freezer until analyzed. Concentrations of salivary free cortisol were measured in duplicate using a commercially available chemiluminescence-immunoassay at the TUD Biopsychology Laboratory in Dresden, Germany. Assay sensitivity was measured to be 0.015 µg/dL. The lower detection limit was 0.41 nmol/L, and inter-assay and intra-assay coefficients of variance were <10 percent.

Three cortisol indices were examined: diurnal cortisol slope, area under the curve with respect to ground (AUCg), and the cortisol awakening response (CAR). Diurnal slope reflects the rate of decrease from highest morning sample to the evening sample. Greater slope values reflect more rapid declines in cortisol levels (lower evening values), whereas smaller values reflect flatter diurnal rhythms (higher evening values). To examine overall cortisol volume, AUCg across day was computed using the trapezoidal method based on hours after awakening (Pruessner et al., 2003). The 30-minute measure was excluded from this calculation as the early morning increase of cortisol is relatively independent from overall cortisol volume (Chida and Steptoe, 2003). Finally, CAR is assessed by the absolute cortisol increase from awakening (averaged across days) to the second cortisol sample (30-minute post-awakening; averaged across days). These parameters characterize the distinctive circadian pattern of cortisol secretion but likely represent different aspects of HPA axis function and may be independently regulated (Clow et al., 2010).

Participants self-reported demographic and disease-related variables.

Data analysis

Hierarchical linear modeling (HLM; HLM 7.0 statistical software program, Supplemental Security Income (SSI) Inc.) was used to examine change in diurnal rhythm over time on an individual basis (i.e. cortisol levels across the day; Bryk and Raudenbush, 1992). Slope of the diurnal change in cortisol levels was calculated by regressing cortisol values on time of day (excluding 30 minutes post-awakening) for each collection day. Cortisol observation times were entered as Level 1 units in the analyses. Sexual functioning, sexual bother, and covariates were entered at Level 2. Multiple linear regression was used to test hypotheses related to CAR and total daily cortisol output. Cortisol parameters were separately regressed on sexual functioning and sexual bother. In post hoc tests, analyses were repeated to control for negative affect to consider the impact of stress-related and/or depressive emotions. All analyses included participant age and body mass index as covariates.

Results

Participants were mostly White (85%), married/partnered (89%), and had at least a 4-year college degree (59%). Most men underwent radical prostatectomy (71%) and 32 percent received radiation treatment, with a small percentage receiving both. The average Gleason score was 5.7 (SD=1.4). Men reported sexual functioning (M=41.50, SD=28.19) and sexual bother (M=57.31, SD=37.69) similar to samples of men treated for localized disease (Gore et al., 2009).

Sexual function and bother and diurnal cortisol indices

Diurnal cortisol slope. HLM revealed that higher sexual bother (t=−2.55, p=.01), but not sexual functioning (t=.53, p=.60), was associated with steeper cortisol slope. The observed cortisol pattern is depicted in Figure 1. Analyses controlling for negative affect did not significantly change the strength or direction of the observed relationships and negative affect did not interact with sexual functioning.

Awakening response. Multiple regression analyses revealed that better sexual functioning (t=.40, p=.04), but not sexual bother (t=−.37,

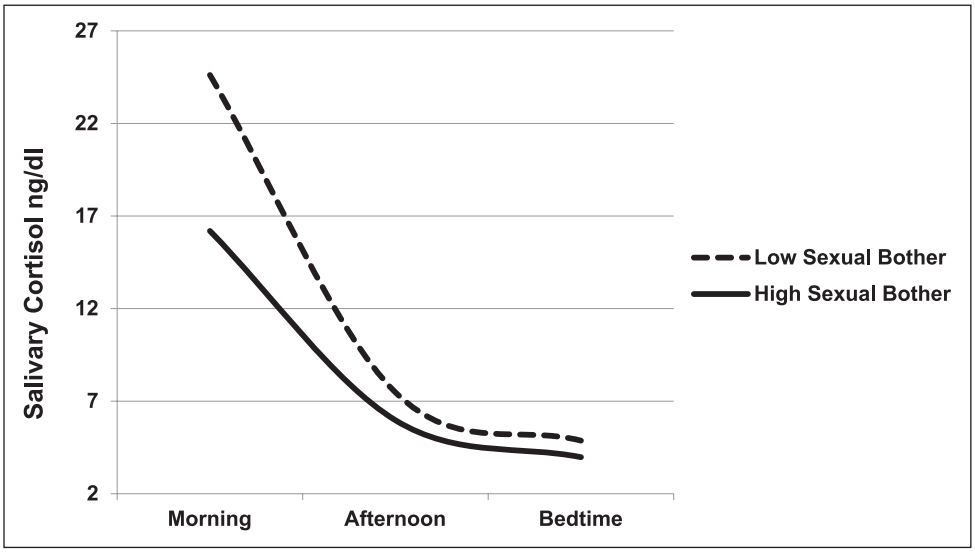

Figure 1. Diurnal cortisol patterns plotted at high (above the median) and low (below the median) levels of sexual bother (median = 38.63). Higher sexual bother was associated with lower morning cortisol levels and overall flatter diurnal slope.

$p = .08$), was significantly associated with CAR. In post hoc analyses controlling for negative affect, sexual functioning was not significant.

Daily cortisol output. Daily cortisol output (averaged across 3 days) was 1.37 ng/dL ($SD = 0.69$). Cortisol data were log-transformed to control for skewness. Neither sexual functioning ($t = -.07$, $p = .45$) nor sexual bother was significantly associated with daily cortisol output ($t = .20$, $p = .62$).

Discussion

Results support a relationship between dysregulation in HPA activity and sexual quality of life after PC treatment. Men who were more bothered by sexual problems exhibited a flatter cortisol slope, with a seemingly blunted morning cortisol level. Flatter slope across the day might reflect a constellation of behavioral symptoms that include depression, fatigue, avoidance, and/or poor sleep (Ancelin et al., 2017; Hoyt et al., 2014, 2016; Schmidt et al., 2016). At the same time, sexual function scores were associated with CAR, whereby men with poorer functioning had smaller morning rises than those with better function.

This is the first known study to document a relationship of CAR and sexual function. CAR reflects the rapid increase in cortisol that occurs 30–45 minutes after awakening. However, its precise function is not well established. It may be uniquely related to health outcomes from other cortisol indices (Golden et al., 2013). CAR may be linked to hippocampal activation to prepare for anticipated stress (Clow et al., 2010). The loss of the significant effect of sexual function on CAR when controlling for negative affect further supports that this relationship may be mediated by an emotional response related to anticipatory stress. Loss of sexual interest was associated with lower ambient plasma cortisol in veterans with post-traumatic stress disorder (PTSD; Lehrner et al., 2016). Future studies should isolate relationships of cortisol patterns with domains of sexual functioning (e.g. libido vs erectile function).

Increasing clinical attention is being given to biobehavioral models of cancer adjustment, stress, and disease course, and dysregulation in the HPA axis is associated with poorer psychological

adjustment and cancer progression (Armaiz-Pena et al., 2013; Fagundes et al., 2017; Giese-Davis et al., 2006). Such biological responses, co-occurring with psychological stress, also have significant potential to affect engagement in treatment providing an adjunctive behavioral pathway (Karvinen et al., 2013). Future research should explore HPA involvement in adherence to penile rehabilitation and injection protocols. Interventions shown to alter HPA axis activity (e.g. physical activity, cognitive-behavioral stress management) may offer contributions to sexual rehabilitation after PC.

In this study, measurements were made at a single point in time. Future work that incorporates repeated measurements of HPA axis activity will better elucidate its mechanistic role and contribute to the specificity of the observed effect. To enhance clinical relevance, understanding the impact of sexual bother at more targeted times in the cancer trajectory will be useful. Notably, sexual bother was measured with a single item. Although this item is a widely used, validated assessment of sexual bother, a multi-dimensional tool might better measure cognitive-emotional responses. Finally, post hoc power analyses revealed adequate power to test the primary hypotheses (>.80), but not differences between radiation and surgical patients. Distinguishing patient subgroups, as well as inclusion of non-cancer controls, is an important next step.

Despite these limitations, this is the first study to show an association between sexual well-being and cortisol in PC survivors. Psychosexual assessment, patient education, and behavioral interventions to reduce psychological bother with sexual problems may be valuable in maintaining patient engagement and physiological regulation after PC treatment.

Declaration of Conflicting Interests

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