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Exploring the relationship between disease-related pain and cortisol levels in women with osteoarthritis

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SUMMARY

Objectives: To determine if (1) Osteoarthritis (OA)-related pain is associated with the diurnal cortisol pattern and cortisol levels; (2) the diurnal pattern of cortisol varies with severity of OA pain and (3) the association between OA pain and cortisol is mediated by daily experience variables (DEV).
Design: In a community-based study of changes in regional and widespread pain among women with OA, participants ($n = 31$) completed daily diaries and collected three saliva samples daily for 7 days. Severity of OA-related pain was assessed by the validated Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. Multilevel regression analyses estimated associations between OA pain and diurnal cortisol levels and slopes, controlling for body mass index (BMI), medication use, time and day. Mediation analyses examined DEV as potential mediators of the association between OA pain and cortisol.
Results: The mean age was 57 years and average BMI 31 kg/m^2. Mean WOMAC pain subscale score was 8.8. Women with higher WOMAC pain scores had higher cortisol throughout the day. The estimated association of WOMAC with cortisol [β 0.083(0.02, 0.15) $P = 0.009$] represents a ~9% increase in cortisol for every unit increase in WOMAC pain score. Women with WOMAC pain scores ≥9 had higher cortisol levels than those with scores <9. Examination of DEV revealed no significant mediated associations between these relationships at the daily level.
Conclusion: In women with OA, disease-related pain is positively associated with cortisol production, particularly with greater pain severity. Future studies should explore biologic mediating variables between OA pain and cortisol.

Introduction

The link between pain (acute or chronic), function of the hypothalamic–pituitary–adrenal (HPA) axis and the subsequent effect on cortisol levels has been well-documented in the literature[1]. Cortisol has important regulatory functions including glucose production, maintenance of the central nervous system, and anti-inflammatory properties that limit the spread of pain[1]. Cortisol release follows a diurnal pattern, with peak levels after waking and a steady decline occurring throughout the rest of the day[2]. The HPA axis is the physiological response of the body to stress with its end role being the release of cortisol from the adrenal glands, the result of a cascade of reactions after the HPA axis is triggered[2]. Pain is a potential stressor and therefore activator of the HPA axis. Depending on the level of threat that an individual associates with the perception of pain, the physiological response may be exaggerated, resulting in cortisol dysfunction[3,4].

Studies of cortisol in people with chronic pain have occurred in a variety of musculoskeletal conditions such as rheumatoid arthritis, low back pain and whiplash[5–7]. In contrast few have examined the association of pain and cortisol in people with osteoarthritis (OA). Besides pain, cortisol dysfunction and OA share several common factors including links with obesity, metabolic syndrome and

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inflammation[8,9]. The experience of pain in OA is known to be intermittent and chronic with the former potentially overlaying the latter[10]. A consequence of intermittent pain flares is hypercortisolism that may lead to obesity, a common comorbidity of OA[11]. In a study of the association of cortisol with acute, chronic (radicular or degenerative low back pain) or intermittent pain (headache), Strittmatter *et al.*[12] compared serum cortisol levels to healthy controls sampled at four separate time points in 24 h. Results showed that those with intermittent pain had the greatest changes in cortisol levels throughout the day[12].

To our knowledge, there has been only one study examining the association between pain and cortisol in people with diagnosed OA. In a study of men with chronic OA pain (defined as OA lasting more than 3 mos and disease process confirmed by Kellgren and Lawrence radiographs) and the association with neuroendocrine function, Khoromi *et al.*[13] reported no difference in mean cortisol levels in both blood and urine compared to healthy controls. Sex differences are known to exist in the response of the HPA axis[14,15] and in regards to pain, this may be due to differences in sex hormones or psychosocial factors[16,17]. However, the association of pain and cortisol in women with OA has not been studied.

Pain mechanisms in OA are currently not well understood and a challenge exists in trying to unravel the discordance found between structural findings typical of the disease and patient reported pain[18]. Given the common factors shared by cortisol dysfunction and OA, along with the greater frequency of the disease in women and concomitant severity of pain[19], it is important to understand the role that the HPA axis and cortisol dysfunction may have in the pain experience of women with OA. The purpose of this study was to determine (1) if OA-related pain is associated with the diurnal cortisol pattern and cortisol levels; (2) if the diurnal pattern of cortisol varies with severity of OA pain and (3) if the association between OA pain and cortisol is mediated by daily variations in pain, fatigue, pain catastrophizing, stress and affect. We hypothesized that there would be a significant association of WOMAC pain with cortisol levels. We further hypothesized that cortisol levels may drop in response to greater pain and that this association may be mediated by any of the daily experience variables (DEV).

Methods

Sample

This is a secondary analysis of data from a community-based study of changes in regional and widespread pain among women with chronic pain in Arizona, USA. The sample was recruited between May 2002 and March 2004 through physician referral, ads in the local newspaper, and posted fliers. Potential participants were screened by telephone to determine eligibility. Eligibility requirements for this analysis included: (1) female; (2) physician-confirmed diagnosis of OA of the hip, knee or spine; and (3) onset of symptoms within the last 5 years or a current pain rating of $\geq$40 on a 0 to 100 scale in the past month. Exclusion criteria were: (1) autoimmune or other comorbid disorders causing widespread pain, inflammation, and fatigue (e.g., fibromyalgia, ankylosing spondylitis) (2) pending litigation regarding the pain condition; and (3) use of daily corticosteroids. The study was approved by the Institutional Review Board at Arizona State University. Participants provided written informed consent for all study activities after completion of the initial eligibility screening and before their physicians were contacted for diagnosis confirmation. The current analysis includes data from 31women with OA who were enrolled in the larger study (final $n = 257$).

Procedures

There were four components to the larger study of women with chronic pain: a daily diary field assessment of symptoms, mood, and cortisol; an in–home assessment of physical and mental health symptoms; laboratory tests of stress reactivity under controlled conditions; and follow-up of illness course after 2 years. Only data from the field and home assessments are used in the current analysis. After initial screening, participants were provided with a laptop computer for completion of daily diary reports before bedtime each evening for up to 7 consecutive days. Reports were time-stamped to verify completion and allowed only one report to be completed per day. Diary questionnaires included measures of pain, pain catastrophizing, fatigue, positive and negative affect, and stress. Over the same period, participants also collected saliva samples three times a day (at 10 a.m., 4 p.m., and 8 p.m.), using cotton salivettes (Sarstedt, Newton, North Carolina). To assess compliance, participants were given a 200-mL bottle with a cap that registered all opening times (MEMS TrackCap, Aardex Ltd., Sion and Zug, Switzerland). Participants were instructed that the bottle was to be opened only at the scheduled collection times and to remove only one swab each time. A digital alarm was set to the scheduled times to serve as a reminder. Participants returned saturated swabs to the salivette tubes, recorded the actual collection time on the tube, and at the end of each day, stored the new samples in their home freezer. In–home clinical assessments were conducted between 1 day and 27 days (mean, 7.0 days) after completion of the daily diaries and saliva collection. At this time, participants also completed questionnaires regarding experiences of OA-related pain. The frozen saliva samples were then taken to the laboratory and stored at -20°C until analysis.

Measures

Salivary cortisol

An in-house radioimmunoassay (Department of Reproductive Physiology, University of Liege) was performed in duplicate on 50 μL of saliva, with salivary free cortisol in competition with a high-performance liquid chromatography preparation of cortisol-3CMO coupled with 2-^{125} iodohistamine as tracer for specific antibodies raised against cortisol-3CMO-BSA[20]. The lower detection limit of the assay was 0.2 nmol/L. The intra- and interassay coefficients of variation were <5% and <12%, respectively. All samples from an individual were analyzed in the same assay to reduce sources of variability. Two cortisol measures had values above the physiological range (>1585 ng/dL)[2] and were excluded from the statistical analysis. Over the 7 days, participants collected a median of 18 valid saliva samples (range, 12–21) with an overall sample of 570 cortisol measures.

Disease-related pain

Severity of OA-related pain was assessed by the valid and reliable Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[21]. The subscale is comprised of five items, scaled from 0 (none) to 4 (extreme). Higher scores indicate greater pain with scores ranging from 0–20[21].

DEV

At the end of each day, participants rated their pain, pain catastrophizing, affect, stress, and fatigue. Mean scores for each measure were calculated across the 7 days for each participant. *Pain* was assessed with the question, “What number describes your average level of arthritis pain today?”. Responses ranges were from 0 (no pain) to 100 (pain as bad as it can be). Pain catastrophizing was assessed using two items from the Coping