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AN EXPLORATORY STUDY OF CHANGES IN SALIVARY CORTISOL, DEPRESSION  
AND PAIN INTENSITY AFTER TREATMENT FOR CHRONIC PAIN

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RUNNING HEAD: Chronic pain and cortisol

## ABSTRACT

*Objective:* To investigate the relationship between cortisol levels, pain intensity and negative mood in chronic pain patients participating in a multidisciplinary pain management programme.

*Patients:* Eighteen chronic pain patients collected saliva samples over several days both directly before and after attending a four-week multidisciplinary pain management programme.

*Outcome measures:* Saliva samples were assayed for their cortisol concentration. Participants also completed self-report measures of pain intensity and depression.

*Results:* Usual pain intensity and waking cortisol levels changed in parallel following treatment, as did changes in depression and cortisol levels late in the morning and in the evening. Depression did not mediate the association between cortisol and usual pain intensity; neither did pain intensity moderate the association between cortisol and depression.

*Conclusions:* Changes in cortisol secretion may provide a useful biological marker of treatment outcome in chronic pain patients after their participation in a multidisciplinary pain management programme.

**KEYWORDS:** chronic pain, cortisol, depression

## INTRODUCTION

Pain that persists despite the application of conventional medical and surgical treatments is disruptive not only in physical terms, but also in broader financial, social and emotional contexts. The psychological and social consequences of chronic pain and disability may evoke a persistent stress response, perhaps exacerbating or maintaining pain [1].

The stress response involves activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Any physical or psychological threat to homeostasis triggers release of corticotrophin-releasing hormone in the hypothalamus, and ultimately raises levels of steroid hormones such as cortisol in the blood stream and saliva [2, 3]. In the short-term, cortisol helps to meet the demands of stress by mobilizing energy stores, and assists recovery from stress by inhibiting further release of corticotrophin-releasing hormone. However, continuing stress promotes maladaptive functioning of the HPA axis which, in turn, may compromise metabolism, impair immune function and alter cardiovascular control [4].

In an early study by Shenkin [5], serum cortisol levels were elevated in patients with pain of a clearly organic etiology but not in patients with pain of a “psychoneurotic or feigned origin” (p1112). The implication of these findings was that cortisol could be used as an indicator of malingering. However, this view remains controversial [6-8]. For example, Lascelles et al. [6] reported that serum cortisol levels were elevated in chronic pain patients, regardless of the etiology of pain. In contrast, salivary cortisol levels after awakening were found to be *lower* in patients with persistent sciatic pain eight weeks after discectomy than in pain-free subjects [9]. Tennant and Hermann [10] reported that serum cortisol levels varied widely in patients

about to participate in a 90-day unimodal opioid treatment program for chronic pain, but normalized following treatment in the majority of participants. The etiology of the shift in cortisol levels is uncertain, because the relationship between cortisol levels, pain and other psychosocial factors was not investigated.

Chronic pain is associated with an array of psychopathology, including depressive disorders, anxiety, personality disorders and substance abuse [11]. For example, the prevalence of major depression in chronic pain patients ranges between 30% and 54% [12]. Major depression is associated with elevated cortisol levels [13], as is negative affect in general [14]. This elevation appears to be driven by stress-induced hypersecretion of corticotrophin-releasing hormone, coupled with failure of negative feedback controls to limit the cortisol response [15]. Thus, cortisol levels might be elevated in a subgroup of chronic pain patients due to depression rather than pain [16]. However, this issue remains unresolved.

The aim of the present study was to investigate the association between cortisol levels, usual pain intensity and depression over the course of a multidisciplinary pain management programme that incorporated cognitive-behavioural techniques to reduce psychological stress [17-19]. In general, reductions in stress and negative affect during various forms of relaxation therapy are associated with reductions in cortisol, both in normal and clinical populations [20-23]. Thus, we hypothesized that decreases in pain and depression following psychological treatment would be associated with decreases in cortisol secretion in chronic pain patients. The longitudinal approach adopted in this study has advantages over a standard cross-sectional design because it allowed us to investigate changes in key variables prospectively. Moreover, we were able to control for the effects of nonspecific aspects of the

procedure, such as anticipatory anxiety or multiple sampling, by comparing changes in cortisol secretion over the course of treatment with changes in pain and depression.

In most previous studies of chronic pain patients [5-8, 10], cortisol concentrations were measured in serum samples. Unfortunately, however, the venesection stress associated with obtaining serum could influence results obtained by this method [24, 25]. Saliva, which contains only the unbound, biologically active “free” fraction of cortisol, is now accepted as a better source for testing cortisol effects than blood [24, 25]. An additional limitation of most previous studies is that samples were obtained during a single day of testing [5-9]. As cortisol is sensitive to random stressful incidents, cortisol should be sampled over several days to average out the impact of these random stressors. Thus, in the present study, salivary samples were obtained for several days before and after patients participated in a multidisciplinary treatment programme for chronic pain.

## METHODS

Participants were recruited on a voluntary basis after their referral and initial assessment for inclusion in the pain management programme. Participants using strong opioid medications or who had received cortisone injections in the previous month were excluded from the study. Twenty-one patients agreed to participate but two dropped out of the study while remaining in the pain management programme. Most participants provided at least 90% of the required saliva samples. However, one participant provided less than 50% of the samples, and thus was excluded from the study. Therefore, a final sample of 18 participants (10 females) completed the study, ranging in age from 18 to 76 years (mean age 44 years) and a median duration of pain of 2.25 years. Fifteen patients suffered from low back, pelvic, neck or

shoulder pain, two had rheumatoid arthritis, and another had post-herpetic neuralgia, thus composing a fairly heterogenous sample. All but four of the patients who entered the study took a range of analgesic, anti-depressant, anti-inflammatory or benzodiazepine medications, and three of the participants were smokers. Participants provided their written informed consent for the procedures, which were approved by the hospital and university ethics committees.

The pain management programme ran for four weeks, with participants attending each weekday morning. Participants attended 2-hour physiotherapy classes each day, consisting of graded exercises such as stretching and walking. They also attended 1-hour psychoeducational seminars twice each week covering topics including medical and psychological information, stress management, cognitive coping techniques, and lifestyle adjustment. In addition, participants attended three 1-hour relaxation training sessions during the programme, and had access to individual psychotherapy as required. An evaluation of the programme in a prospective controlled cohort study indicated that gains were made in terms of depression, disability and pain [17].

Pain perception was assessed using a simple 0 (no pain at all) to 10 (worst pain imaginable) Numerical Graphic Rating Scale (NGRS) of usual pain intensity, while depression was assessed using the Zung Self-Rating Depression Scale (ZSDS) [26, 27]. In addition, participants completed the Roland-Morris Disability Questionnaire [28], the MOS 36-Item Short Form (SF-36) to assess functional health status and health-related quality of life [29], and reported on their current medication intake. A Medication Quantification Scale (MQS) score that represented total medication usage was calculated using weights assigned by medication class and dosage [30]. Participants completed the self-report inventories on the

first and last days of their participation in the pain management programme, based on their experiences over the previous week.

Participants provided saliva samples on the three days immediately before participating in the pain management programme, and the three days immediately after completing the treatment. They were asked not to eat or drink anything containing caffeine or alcohol, or smoke cigarettes, in the 30 minutes before providing a sample because these substances may influence cortisol secretion directly, or might influence cortisol secretion indirectly by altering saliva pH [31-33]. Participants provided saliva samples four times each day: upon waking; late morning (11 a.m.); in the afternoon (4 p.m.); and just prior to going to bed (not later than 11 p.m.).

Samples were collected using cotton dental rolls, which participants then placed in 5 mL plastic tubes with screw-capped lids and stored in their home freezer. Samples were usually defrosted when delivered by participants to the experimenter at the hospital, but cortisol concentration in saliva samples is unlikely to deteriorate as a result of temporary defrosting [24, 34]. The samples were stored at approximately  $-20^{\circ}\text{C}$  until the completion of the sample collection period. They were then assayed by an enzyme-linked immunosorbent assay based on the general protocol of Elder and Lewis [35]. The cortisol conjugate used was hydrocortisone – 3 CMO-BSA; (Steraloids; Q3889); the primary antibody to cortisol was anticortisone (Sirosera; C336) and the secondary, enzyme-linked antibody was donkey-anti sheep-HRP (Sigma; A3415). The intra and inter-assay coefficients of variation were 10.4% and 9.1% respectively.



The cortisol concentration data (in ng/mL) was log transformed prior to data reduction and statistical analysis to reduce the effect of outliers and to achieve adequate normality of the positively skewed data. Changes from before to after treatment were investigated for each dependent variable with paired t-tests using the SPSS package (version 10). The association between the pre-to-post treatment change in log-transformed cortisol levels and change in psychometric ratings was investigated with Pearson's correlation coefficient and partial correlation coefficients. All inferential statistics were two-tailed.

## RESULTS

Mean ratings before and after treatment are shown in Table 1, and mean log-transformed cortisol levels before and after treatment are shown in Table 2. Decreases in the Disability Quotient and increases in SF-36 scores (reflecting increases in health-related quality of life) indicate that the treatment was effective in these domains. Although depression, pain ratings and cortisol levels did not change significantly after treatment in the group as a whole, there was substantial variation among participants in all measures, particularly cortisol, both before and after treatment. Inspection of the raw data indicated that many participants regularly experienced very high levels of cortisol, often with clear disruption of the expected diurnal pattern, while others experienced consistently low levels. Since pain and depression improved after treatment in some but not all cases, individual differences in cortisol levels before treatment, and changes following treatment, were explored in relation to depression and pain.

### Association between cortisol levels, pain and depression before treatment

Initial data analysis revealed an association between age and cortisol levels at each time of day (ranging from  $r=0.37$  to  $0.58$ ). Moreover, usual pain intensity was greater in older than younger participants [ $r(16)=0.60$ ,  $p<0.01$ ]. However, there was no association between medication consumption (as reflected by the MQS scores) and cortisol levels at any stage of the study. Therefore, only age was entered as a covariate in analyses that investigated the association between cortisol levels and other variables. As shown in Table 3, waking cortisol levels correlated strongly with pain ratings, but this relationship diminished to only a moderate relationship when the effect of age was removed [ $r(15)=0.39$ , not significant]. The relationship did not change when depression was entered as an additional covariate. Cortisol levels were not associated with depression at any time of day, either before or after usual pain intensity was entered as a covariate.

#### Association between post-treatment changes in cortisol, pain and depression

The change in cortisol levels from pre- to post-treatment was calculated separately for each of the times sampled during the day. Both before and after controlling for age, post-treatment changes in waking cortisol levels were associated with changes in pain (Table 4). As shown in Figure 1A, reductions in pain over the course of treatment were generally associated with reductions in waking cortisol levels. The relationship between post-treatment changes in waking cortisol levels and changes in usual pain intensity [ $r(16)=0.62$ ,  $p<0.01$ ] persisted after controlling for changes in depression [ $r(15)=0.63$ ,  $p<0.01$ ]. The relationship did not change after age was entered as an additional covariate [ $r(14)=0.56$ ,  $p<0.05$ ], but decreased after the most responsive patient was excluded from the analysis [ $r(13)=0.22$ , not significant].

Post-treatment reductions in late morning cortisol levels were generally associated with reductions in depression (Table 4 and Figure 1B). This effect persisted after controlling for changes in usual pain intensity [ $r(15)=0.60$ ,  $p<0.05$ ], and emerged for evening samples when age was entered as an additional covariate [for morning samples,  $r(14)=0.70$ ,  $p<0.01$ ; for evening samples,  $r(14)=0.69$ ,  $p<0.01$ ].

## DISCUSSION

This exploratory study produced a number of findings with interesting implications for understanding cortisol secretion in relation to usual pain intensity and mood in chronic pain patients. In particular, an association between the usual intensity of chronic pain and salivary cortisol levels upon waking was detected. In addition, post-treatment changes in waking cortisol levels were associated with changes in usual pain intensity, as were post-treatment changes in late morning and evening cortisol levels and depression.

Previous studies [5-8] differentiated between pain conditions of a mainly physical or psychosocial etiology on the basis of cortisol levels, and Shenkin [5] concluded that a low cortisol level was indicative of malingering. However, the effects of pain intensity, venesection stress and mood on cortisol levels were not considered in these studies.

Furthermore, the relationship between age and cortisol levels was overlooked, as was day-to-day variation in cortisol. We attempted to minimize the impact of these factors by sampling salivary cortisol several times per day for several days before and after patients participated in a pain management programme. In addition, the relationship between cortisol levels, pain and depression was investigated independently of age. The present findings indicated that an association between waking levels of cortisol and usual pain intensity was independent of

depression but was influenced by the participant's age. Cortisol levels varied widely between individuals and when measures were repeated in the same individual, both in the present study and in previous research [10]. Thus, it seems unlikely that psychosocial disorders such as malingering could be identified purely on the basis of the patient's cortisol levels.

Pain intensity was linked most closely with cortisol levels upon waking, possibly because cortisol begins to peak at this time of day or because of minimal interference by confounding factors such as daily hassles, eating, drinking, smoking and medication on cortisol and pain. A similar association between pain and waking levels of cortisol was identified recently by McLean et al. [36] in fibromyalgia patients. Pain itself, or emotional responses to pain, may generate activity in the hypothalamic-pituitary-adrenal axis [4, 36]. Alternatively, neuro-immune responses in the periphery associated with pain could stimulate cortisol release [37]. Cortisol might also influence pain intensity by acting on glucocorticoid receptors that interact with serotonergic or adrenergic pain modulation processes in the central nervous system [36]. An additional interesting possibility is that stress-related elevations in cortisol are involved in the pathogenesis of chronic pain – while in the short-term cortisol has anti-inflammatory properties, at chronically high levels cortisol has deleterious effects on the immune system [38], skeletal muscle tissue [39], and bone density [40, 41]. Thus, treatments that reduce stress-evoked elevations in cortisol might help to curb further physical deterioration in chronic pain patients.

Hyperactivity of the hypothalamic-pituitary-adrenal axis is a feature of major depression [42], and may also be associated with negative affect in non-clinical samples. For example, Pruessner et al. [43] recently identified an association between depressive symptomatology and waking cortisol levels in healthy young men. This association was not detected in the

present study, perhaps because ongoing pain or other factors (e.g., inflammation, medication or degenerative processes) also influenced cortisol secretion. Alternatively, the association may have been masked by heightened variability in cortisol levels at this time of day [44].

Although cortisol secretion before the pain management programme was unrelated to levels of depression, *changes* in depression over the course of treatment were associated with changes in cortisol secretion in the morning and evening, independently of changes in pain. Similarly, changes in pain over the course of treatment were associated with changes in waking levels of cortisol secretion, independently of changes in depression. In contrast to pain, the relationship between negative affect and cortisol secretion may strengthen during the day, due to the impact of daily hassles on mood. Taken together, the findings suggest that investigating changes in cortisol levels within the same individual over time may be more useful than investigating individual differences in cortisol secretion at a single point in time, particularly in the context of treatment where reductions in usual pain intensity and improvements in mood may be associated with reductions in salivary cortisol levels.

This study was limited by its small and heterogenous sample and its correlational design, and thus was exploratory in scope; hence, replication with more rigorous experimental controls and larger sample sizes would be required to minimize the impact of outliers and to identify causality in the relationships observed here. To better understand the relationship between the immediate experience of pain and cortisol secretion, the association between salivary cortisol and momentary fluctuations in pain, mood, stress and anxiety in chronic pain patients should be explored more closely [45]. This is of particular interest given the frequent aberrant deviations from the expected pattern of diurnal variation observed in many of the participants in the present study.

Despite the limitations of this research, the present findings provide preliminary evidence of a relationship between waking cortisol levels and usual pain intensity, independent of depression. This relationship appeared to be stronger within than between individuals, presumably because psychological or physiological factors that influence pain ratings and cortisol secretion masked the association when investigated across the study population. The findings suggest that changes in cortisol secretion may provide a useful biological marker of treatment outcome in chronic pain patients, both in terms of mood change and change in usual pain intensity.

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Table 1: Results of psychometric outcome measures pre- and post-treatment (n=18).

Psychometric Instrument	Pre-treatment		Post-treatment		t-test	Sig.
	Mean	SD	Mean	SD		
ZSDS	31.22	14.31	28.78	12.3	1.08	0.296
NGRS	5.17	1.79	4.06	1.73	1.99	0.063
SF-36	321	160	395	151	2.97	0.009*
DQ	10.00	4.60	7.44	5.14	2.95	0.009*
MQS	8.71	11.92	6.65	8.78	1.73	0.103

ZSDS: Zung Self-Rating Depression Scale; NGRS: a 0-10 Numerical Graphic Rating Scale

of average pain perception intensity; SF-36: MOS 36-Item Short Form; DQ: Disability

Quotient; MQS: Medication Quantification Scale.

\* statistically significant ( $p < 0.05$ ) after applying the Bonferroni correction for multiple comparisons across the five dependent variables.

Table 2: Log-transformed cortisol concentrations (initially measured in ng/mL) pre- and post-treatment (n=18).

Sample Collection	Pre-treatment		Post-treatment		t-test	Sig.
Time	Mean	S.E.	Mean	S.E.		
Wake	1.12	.12	1.07	.11	.40	0.70
Late morning	.72	.14	.73	.16	.06	0.96
Late afternoon	.73	.15	.57	.14	1.31	0.21
Bedtime	.50	.17	.47	.19	.23	0.82

Table 3: Pearson's correlation coefficient between pain, depression  
and pre-treatment levels of cortisol

	Cortisol (Time of Sampling)			
	Wake	Late Morning	Late Afternoon	Bedtime
ZSDS	-0.27	-0.38	-0.45	-0.38
NGRS	0.59**	0.25	0.30	0.45

ZSDS: Zung Self-Rating Depression Scale; NGRS: a 0-10 Numerical Graphic Rating Scale of average pain perception intensity.

\*\*  $p < 0.01$ ; statistically significant ( $p < 0.05$ ) after applying the Bonferroni correction for multiple comparisons across the two dependent variables, or across the four time points within each dependent variable.

Table 4: Pearson's correlation coefficient between post-treatment changes in cortisol levels and changes in pain and depression

	Cortisol (Time of Sampling)			
	Wake	Late Morning	Late Afternoon	Bedtime
ZSDS	0.12	0.60**	0.11	0.43
NGRS	0.62**	0.16	0.11	0.04

ZSDS: Zung Self-Rating Depression Scale; NGRS: a 0-10 Numerical Graphic Rating Scale of average pain perception intensity.

\*\*  $p < 0.01$ ; statistically significant ( $p < 0.05$ ) after applying the Bonferroni correction for multiple comparisons across the two dependent variables, or across the four time points within each dependent variable.

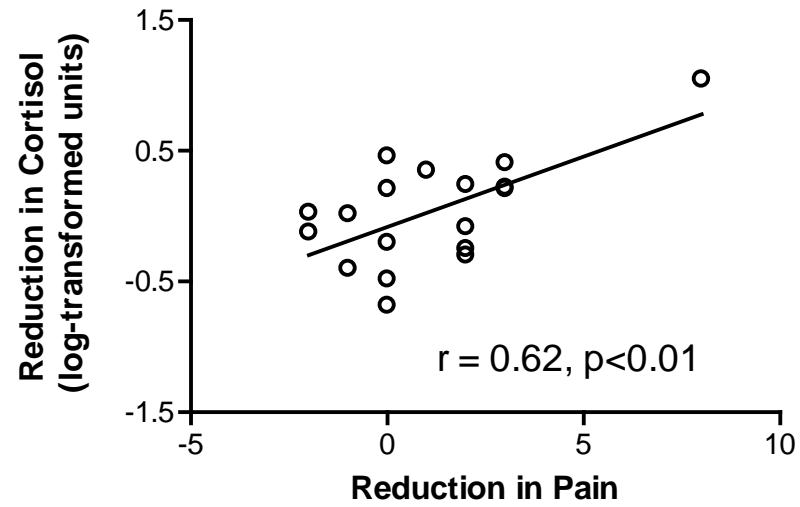
### Figure legend

Figure 1. Relationship between changes in pain and waking cortisol (A), and depression and morning cortisol (B), over the course of treatment. Reductions following treatment were calculated by subtracting post-treatment levels from pre-treatment levels.



## Effect of treatment on pain, depression and cortisol

### A. Waking Cortisol and Pain



### B. Morning Cortisol and Depression

