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Diurnal Variation of Cortisol in People with Dementia: Relationship to Cognition and Illness Burden

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Introduction

People with advanced dementia have impaired immune function, impairments in cognition, and a decreased tolerance for physical, environmental, and psychosocial stressors.^{1,2} Because physical, environmental, and psychosocial stressors activate the hypothalamic-pituitary-adrenal (HPA) axis to increase the secretion of cortisol, alterations in HPA axis function may in turn have an impact on physical and emotional responses to stressors and further compromise physical and cognitive status.³ The purpose of this study was to describe the diurnal rhythm of cortisol in people with advanced dementia and examine differences in mean cortisol level, and the slope and pattern of the cortisol rhythm associated with cognition and illness burden.

The cortisol diurnal rhythm is robust and persists from infancy to old age.^{4,5} A typical diurnal rhythm of cortisol is characterized by a peak after waking followed by a decline in levels throughout the day.⁶ While the normal diurnal rhythm of cortisol is well-established, individual variability has been documented. Physical, environmental, and psychosocial factors have been associated with changes in cortisol diurnal pattern. Alterations have been found in disease states such as rheumatoid arthritis,⁷ depressive symptoms,⁸ Alzheimer's disease,^{9–10} and fibromyalgia.¹¹ Environmental and psychosocial factors associated with changes in diurnal rhythm include living in a circumpolar region,¹² shift work,¹³ daily hassles,¹⁴ military survival training,¹⁵ and child maltreatment.¹⁶

Although most healthy older adults have normal circadian rhythms,⁵ dampened patterns were reported in 2% and 17% of two samples of community dwelling older adults.^{17,18} Dampened patterns were found in 69% of older adults with complaints of memory deficits and/or depressive symptoms.⁸ Flattening of the cycles usually occurs because of an elevated afternoon cortisol rather than a decreased morning cortisol.^{19,20} Fiocco et al.⁸ found that

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19% of 42 depressed participants had a typical negative slope on the first week of sampling, followed by a flattened pattern the next week.

Changes in cortisol pattern that reflect altered HPA axis activity may have deleterious effects on health outcomes.^{3,21} However, it is still unclear if cortisol level, slope, pattern or consistency of pattern has the most significant impact on health.²¹ Sephton, et al.²² found that a flatter cortisol slope was associated with an increased risk of mortality in a study of 104 women with metastatic breast cancer. Flatter cortisol slopes were associated with low counts and suppressed activity of circulating natural killer (NK) cells.

Methods

Study Design and Participants

The current report used only baseline data from an experimental study that examined the effects of a nursing assessment and treatment protocol.²³ Two days of baseline data were collected one week apart on a weekday. The convenience sample consisted of 117 participants from twelve nursing homes (NHs) that had a typical schedule of early waking and early bedtime. No obvious or unusual stressors such as renovations or major changes in staffing were present in the NH prior to data collection. Inclusion criteria were as follows: a diagnosis of a dementing illness; no chronic psychiatric diagnosis other than dementia; no known pituitary or adrenal diseases; were not taking corticosteroids; a length of stay of at least 4 weeks to control for relocation stress; and no acute illness. The study was approved by the Institutional Review Board. Written consent was obtained from the guardian and verbal assent from the participants.

Measures

Activity of the HPA axis was assessed by measuring cortisol in saliva samples collected using three hydrocellulose microsponges.²⁴ Salivary cortisol is in equilibrium with the free (unbound) cortisol in plasma, and is a direct reflection of plasma free cortisol,²⁵ and as such is now an accepted measure used to assess biologically active (unbound) cortisol²⁶ and stress.^{27,28}

Cognition and illness burden were assessed once using the Mini-Mental State Examination (MMSE) and the Cumulative Illness Rating Scale -Geriatric (CIRS-G)^{29, 30}. The MMSE is a screening tool with a range of 0 to 30, and lower scores indicative of more severe impairment. The CIRS-G measures chronic medical problems by rating 14 organ-system categories along a 4-point rating of severity with a possible range of 0 to 54. Higher scores indicate more severity of illness. For post hoc analysis of case issues and possible covariates, types of medications taken and waking times were recorded.

Procedures

Two research assistants were trained to screen for eligibility, administer the MMSE, review the charts for medications and illness burden (CIRS-G), and to collect the saliva samples. Following consent and eligibility testing, all MMSE and CIRS-G were completed in week 1 and Week 1 saliva samples were collected. Week 2 saliva samples were collected one week later.

Four saliva samples were collected per day one week apart. Samples were collected (± 15 minutes) from under the tongue 30 minutes after waking (T1-waking), 45 minutes after breakfast (T2-morning), and 45 minutes before (T3-afternoon) and after dinner (T4-evening). There is well-documented literature supporting the use of a similar physiological stimulus such as food intake during regular mealtimes to stimulate the HPA axis and control

for some intra-individual variation in diurnal rhythm.^{31, 32} Because participants of many NHs retire to bed early in the evening, 45 minutes after dinner was a feasible T4 evening data collection time.

Food and fluid intake were prevented for 30 minutes and smoking was prevented for 60 minutes prior to the saliva collection. Specimens were not collected within 3 days of major dental work to prevent blood contamination, and were collected at least 30 minutes past the time of any potentially confounding events such as bathing or a medical exam. At least 15 minutes prior to sample collection, plain water and an untreated oral swab were used to swab the mouth, paying attention to debris removal. Following collection, samples were inserted into a cryogenic vial or storage tube, centrifuged, batched by participant, and frozen at -20°C prior to assay and further analysis.

Salivary cortisol was measured using an ELISA (Salimetrics, LLC, State College, PA), according to the manufacturer's protocol.³³ All samples from the same participant were run in the same batch to avoid between batch variability. The intra-assay coefficients of variation (CV) were 5.2% at 3.1 (SD, 0.2) nmol/L ($n = 10$) and 2.6% at 10.4 (0.3) nmol/L ($n = 10$). Inter-assay (total) CVs were 11% at 2.8 (0.3) nmol/L ($n = 10$), 11% at 10.1 (1.1) nmol/L ($n = 10$), and 6.9% at 25.0 (1.7) nmol/L ($n = 10$).³¹

Data Analysis

Log transformations of cortisol measurements were used to induce normality; as a result, the data were summarized using geometric means and 95% confidence intervals. From these data, waking cortisol (T1), morning cortisol (T2), afternoon cortisol (T3), evening cortisol (T4), slope (least squares curve to the four data points for each participant), and area under the curve (AUC) were calculated. Adjustments for covariates (such as the use of narcotics or benzodiazepines and waking time) were tested and were not significantly associated with any outcomes. Therefore, the final results reflect univariate ANOVA models, Pearson's correlations and t-tests. Given the large number of cortisol measurements tested, the two outcome variables of cognition and illness burden, and the two days of data, an ad-hoc adjustment of the significance level of 0.01 was used. From the sample of 111, the number of participants having complete cortisol data available for each statistical analysis varied somewhat. The number of participants included in each analysis is listed in the corresponding table.

Examination of patterns of cortisol concentrations revealed three different trends or subsets of cortisol patterns. Definitions for the patterns were established after examining the individual patterns of cortisol including a consideration of error variations and previous literature.^{17, 18, 34} Relatively flat patterns were defined as a ratio of morning to evening cortisol levels < 2 . A negative slope pattern was defined as the value at T3 (afternoon) $\leq 20\%$ of morning cortisol levels. An afternoon increase was defined as a cortisol level at T3 $> 20\%$ of morning cortisol levels.

Results

Of the planned 936 saliva sample collections from 117 participants over two study weeks, there were 26 instances (2.8%) in which participants refused saliva sample collection. For an additional 12 planned collections (1.3%), saliva samples were not collected for a variety of reasons including out of the NH, placed on corticosteroids, or the intervention protocol started before Week 2 data collected. Forty-four samples (4.9%) did not have sufficient quantity for assay. Hence, a total of 854 (91%) of the samples were available for analyses.

Cortisol samples from 6 participants had very high concentrations (i.e. > 90 nmol/L), were considered outliers, and investigated for contamination with exogenous steroids.²⁸ These samples were analyzed for cortisol and cortisone concentration by liquid chromatograph/tandem mass spectrometry.³⁵ All samples were contaminated with exogenous hydrocortisone. All 44 samples from these 6 participants were dropped from the study reducing the number of samples to 810 samples from 111 participants.

The sample of 111 participants was primarily white (99%; $n = 110$), female (77%; $n = 86$), educated (mean years = 12.1, $SD = 2.7$; range 4–20) and severely demented ($M = 6.81$, $SD = 6.0$; range 0–23). The average age of participants was 87 ($SD = 7$), and the length of stay in the NH averaged 33.2 months ($SD = 28.6$, range 2–125). More than 50% ($n = 56$) of the sample had 9 or more co-morbid conditions and 9% ($n = 10$) had 4 or more body systems rated for illness as severe or extremely severe (CIRS-G $M = 14.74$, $SD = 4.75$, range 4–33).

Thirteen (12%) participants were taking a narcotic and 25 were taking a benzodiazepine medication at baseline. Wake time ranged from 5:00 am to 8:00 am.

Cortisol Diurnal Rhythm

As seen in Table 1, cortisol levels were generally highest 30 minutes after waking, and decreased through the day). The awakening and evening measurements were weakly correlated ($r = 0.172$, $p = 0.088$ at Week 1 and $r = 0.26$, $p = 0.01$ at Week 2). Awakening cortisol and AUC were more strongly correlated ($r = 0.51$, $p < 0.001$ at Week 1 and $r = 0.44$, $p < 0.001$ at Week 2).

Examination of patterns of cortisol revealed that the majority (55%) exhibited a negative slope, 38% had a relatively flat pattern and 7% exhibited an afternoon (T3) increase. Table 2 describes the consistency in the type of cortisol pattern between Week 1 and Week 2. Thirty-eight (39%) of participants had a consistent negative slope pattern, 13 (13%) had a consistent flat pattern and 2 participants (2%) had a consistent afternoon increase. Chi Square test of association between weeks 1 and 2 was not statistically significant. Forty-four participants (45%) had an inconsistent pattern.

Relationship of Cognition and Illness Burden to Cortisol

Differences in MMSE and CIRS-G scores based on cortisol pattern are presented in Table 3. Those with a relatively flat pattern had the lowest MMSE scores and those with the afternoon increase in cortisol had the highest illness burden scores, but the trends did not reach a level of statistical significance. The relationship between cortisol measurements, cognition and illness burden are presented in Table 4 but were not statistically significant after adjusting for multiple testing. Differences in MMSE and CIRS-G between those who did and did not have a consistent pattern between Week 1 and 2 were compared and there were no statistically significant differences ($t(2,93) = .080$, $p = .937$ for MMSE and $t(2,93) = .482$, $p = .631$ for CIRS-G).

Discussion

This study examined differences and variability in diurnal rhythm of cortisol in a sample of NH participants with advanced dementia. Three distinctive patterns of diurnal cycles were identified: those in which cortisol decreased during the day, those in which cortisol did not change > 20% during the day, and those in whom cortisol initially decreased but then increased in the afternoon. The finding that the majority of participants exhibited a normal negative slope supports the robustness of the diurnal pattern even in the face of advanced dementia.³⁴

A flattening of the slope is consistent with the hypothesis that HPA axis dysregulation occurs with increased frailty burden and decreased resiliency.^{21, 36} Stone et al.³ reviewed four studies of adults, all which showed subgroups with a flattened diurnal rhythm.

The finding that some participants exhibited a pattern of peak morning cortisol, followed by a decline and subsequent afternoon increase in cortisol, is consistent with others who have found small subgroups with an increase late in the day.³⁷ Elevated cortisol late in the day, resulting in a flattened rhythm, may be indicative of an acute stressor or HPA axis dysregulation. It has been suggested that elevated cortisol secretion late in the day is associated with a decreased sensitivity of the HPA axis to negative feedback with aging.³⁷

The stability and rhythmicity of diurnal patterns may prove important to our understanding of the vulnerability of different individuals to environmental and psychosocial stressors that may contribute to negative health consequences such as depression, cognitive impairment and other chronic diseases (e.g. cardiovascular disease, Type II diabetes).³⁸ The negative slope pattern was consistent for 39% and the flat groups were consistent from Week 1 to Week 2 for 13%. In this study the group with relatively flat slopes had absolute values of cortisol that were not particularly high or low. Stable low flat rhythms are thought to be more deleterious to health, as this dysregulation in the HPA axis could have an impact on the response to physical, psychosocial and environmental stressors.³ Inconsistent rhythms may be more indicative of a reactive and less stable HPA axis. Impaired HPA axis responses to stressors are hypothesized to initiate or amplify alterations in many physiological systems, including the endocrine, immune, cardiovascular and skeletal systems.^{36, 39}

The lack of association between cortisol pattern MMSE and illness burden is inconsistent with previous studies.^{36, 40, 41} This sample had advanced dementia and the validity of the MMSE at the low end of the range has been questioned and may have influenced results. The lack of statistically significant association between cortisol and illness burden could indicate habituation to the stress of the chronic conditions or measurement error, confounding influences or subject heterogeneity.

While this study contributes to understanding of differences in the diurnal pattern of cortisol for older adults with dementia, more research is needed to understand the etiology of the differences and the biological mechanisms involved. In addition, research is needed to understand factors associated with individual differences in diurnal pattern and the possible health consequences of these differences. If future research confirms the stability of the patterns in subgroups of people with dementia, diurnal pattern variation may be important in understanding the differential effectiveness of treatments and targeting treatments more appropriately for those most at risk. The sundowning phenomenon often observed in some people with dementia involves increased agitation in the late afternoon or early evening,⁴² and may be related to differences in cortisol diurnal pattern.

Given that this study involved collecting samples from a group that can be difficult to recruit and retain, it is encouraging that the numbers of samples that could be collected in a sufficient quantity was high and that the refusal rate for collection was relatively low. Also consistent procedures were used to collect samples in the same manner and from the same location in the mouth. We investigated for possible medication error or exogenous hydrocortisone in skin products used by the six participants with contaminated samples and could not find any likely source for the contamination. The question remains of how these NH participants were exposed to unknown sources of exogenous hydrocortisone. The question is particularly salient because corticosteroids are associated with many side effects.

Limitations of this study are acknowledged. Four cortisol samples were collected daily on only two days that were one week apart. Thus, a number of factors may have intervened in

the ensuing week that affected the consistency of cortisol diurnal rhythm from Week 1 to Week 2. While one day does provide information about a diurnal rhythm in healthy elderly subjects, it is unclear if the same holds true in the NH population with advanced dementia. It would be helpful to replicate this study with a larger sample, more consecutive days of data collection and a healthy elderly comparison group.

Conclusion

This study provides initial evidence of individual variations in diurnal pattern of cortisol secretion and the stability of these patterns in NH residents with dementia. Calculating group averages without consideration for diurnal rhythm can obscure results and impede advances related to the contribution that an altered cortisol diurnal rhythm may make to individual vulnerability. The delineation of diurnal cortisol patterns in people with dementia adds to our understanding of cortisol as a biomarker, and suggests that incorporating measures of these patterns into dementia research as moderating and mediating variables may be useful.

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Table 1
Geometric Mean Cortisol Levels and 95% Confidence Intervals in Week 1 and 2 by Time of Day

Time of Day	Week 1				Week 2			
	n	Mean	Lower	Upper	n	Mean	Lower	Upper
Awakening	106	9.01	8.07	10.06	101	10.78	9.59	12.12
Mid-morning	104	7.46	6.68	8.33	101	7.33	6.48	8.29
Afternoon	100	5.23	4.57	5.99	99	5.20	4.61	5.86
Evening	102	5.05	4.41	5.78	100	4.92	4.36	5.56

Table 2

Frequency Distribution of Cortisol Patterns from Week 1 to Week 2

		Week 2		Flat	Negative Slope	Evening Rise	Total
Week 1	Negative Slope			10	38	6	54
	Flat			13	16	7	36
	Evening Rise			1	4	2	7
	Total			24	58	15	97

Chi Square = 7.28, p = .122

Table 3

Differences in Cognition and Illness Burden Based on Cortisol Pattern

Cognition	Pattern	n	Mean	SD	F	p-value
Week 1	Negative Slope	56	7.37	5.82		
	Flat	39	5.74	6.45	0.84	0.436
	Afternoon Increase	7	6.86	5.58		
Week 2	Negative Slope	60	7.62	5.92		
	Flat	24	4.08	4.28	3.28	0.042
	Afternoon Increase	16	6.44	6.76		
Illness Burden	Pattern	n	Mean	SD	F	p-value
Week 1	Negative Slope	56	16.77	4.41		
	Flat	39	18.03	4.24	1.42	0.246
	Afternoon Increase	7	19.14	7.03		
Week 2	Negative Slope	60	17.1	4.33		
	Flat	24	17.96	5.16	0.86	0.426
	Afternoon Increase	16	18.69	4.85		

Table 4
Relationships between Cortisol Measurements, Cognition and Illness Burden

Cortisol Measurement	Cognition			Illness Burden		
	n	r	p	n	r	p
Week 1	Log (cortisol)					
	T1	106	-0.063	0.521	106	-0.182 0.061
	T2	104	-0.024	0.808	104	-0.058 0.557
	T3	100	-0.058	0.57	101	0.089 0.376
	T4	102	-0.056	0.573	102	0.128 0.199
	AUC	92	-0.023	0.829	92	0.78 0.78
Week 2	Slope					
		92	-0.039	0.711	92	0.217 0.038
		n	r	p	n	r p
	T1	101	-0.003	0.978	101	-0.061 0.542
	T2	101	-0.035	0.728	101	-0.01 0.918
Week 2	T3	99	-0.165	0.103	99	-0.018 0.862
	T4	100	-0.167	0.096	100	0.039 0.7
	AUC	91	-0.128	0.225	91	-0.035 0.741
	Slope	91	-0.229	0.029	91	0.047 0.661