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Intraindividual Cortisol Variability and Psychological Functioning in Caregivers of Hematopoietic Stem Cell Transplant Patients

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Abstract

Objective—Caregiving for allogeneic hematopoietic stem cell transplant patients (Allo-HSCT) carries a significant psychological burden yet it remains unclear whether Allo-HSCT caregivers demonstrate disruptions to stress systems, such as hypothalamic pituitary adrenal axis. Greater intraindividual cortisol variability (ICV) has been observed in psychiatric disorders; however, there is a knowledge gap evaluating ICV in caregivers. We predicted greater ICV would be related to poorer mental health in Allo-HSCT caregivers.

Methods—Allo-HSCT caregivers (n=140) collected saliva for 3 consecutive days at 4 time points/day. Psychological variables included sleep quality and a summary composite score of overall mental health.

Results—Regression analyses demonstrated that greater ICV was significantly related to poorer overall mental health ($\beta = .25$; $p = .009$), while poorer sleep did not reach significance ($\beta = .16$; $p = .069$). No significant relationships emerged for the cortisol area under the curve, diurnal decline or awakening response.

Conclusions—Results extend prior work examining ICV as a unique marker that is possibly more sensitive than other widely applied measures of HPA-axis dysregulation to a distressed population of caregivers.

Introduction

Caregivers are a particularly distressed population [1, 2]. Cancer patients' caregivers, specifically, also have been observed to bear significant psychological burden [3] and indeed, this population often reaches clinical cutoff criteria for psychiatric conditions such

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CONFLICTS OF INTEREST

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as anxiety and depression [4, 5]. However, it remains less clear how these psychological factors might be related to changes in physiologic regulation, such as the hypothalamic-pituitary-adrenal (HPA) axis. One report suggests that caregivers of brain cancer patients demonstrate dysregulated sympathetic nervous system activity and elevated inflammatory processes compared to controls; however, this research did not demonstrate a difference in cortisol as measured by total output or diurnal rhythm [6]. Thus, it is germane to examine other approaches to quantifying HPA-axis regulation in this population.

Cortisol output over a day corresponds to a sinusoidal pattern [7] and is often collected in saliva across multiple time points within and across days to more accurately capture an individual's typical diurnal rhythm. Many advocate for selecting statistical approaches, such as mixed models[8], that account for the nested data structure of cortisol (e.g., times within day and days within people) given their flexibility with unequally spaced time points, handling of missing data and allowance for varying intercepts and slopes [9, 10]. However, an additional benefit of such approaches is their ability to capture variability *within* individuals. Termed intraindividual cortisol variability (ICV), this approach is independent of diurnal linear slope that is related to important clinical outcomes [11, 12]. It eliminates time-structured variability and isolating *net* intraindividual variability[13] captured in short periods of time, such as multiple days of salivary cortisol sampling. Recent work applying ICV suggests that while the slope of the cortisol diurnal decline was not related to mild depressive symptoms in a group of women undergoing surgery for cancer, greater ICV was associated with greater depressive symptoms [14]. Similar calculations, extracting intraindividual error terms from diurnal cortisol rhythms in psychiatric populations compared to controls, demonstrate less predictable cortisol output related to those with remitted bipolar disorder [15] and major depressive disorder [16]. Collectively, compelling evidence that psychological factors may be related to ICV but no research to date has examined ICV in relationship to stress in caregivers.

Allogeneic hematopoietic stress cell transplant (Allo-HSCT) caregivers exhibit significant stress, anxiety and poor sleep compared to established norms [17] before the patient's transplant and their assuming of full caregiving responsibilities. The purpose of the present study was to examine possible relationships between psychological functioning and ICV in caregivers of Allo-HSCT patients prior to patient transplantation. It was hypothesized that poorer sleep and worse mental health would be associated with greater ICV. A secondary aim was to compare ICV to other widely utilized cortisol outcomes (e.g., cortisol diurnal slope, area under the curve with respect to ground, and cortisol awakening response).

Methods

Participants

Allo-HSCT caregivers were recruited sequentially (n=268 approached) from a community hospital between November 2008 and April 2012 and 148 dyads were consented for participation in a randomized clinical trial providing stress management. Inclusion criteria included caring for an allo-HSCT patient the first 100 days post-transplant (at least 50% of the caregiving responsibilities), ability to speak and read English, at least 18 years old and with telephone access. Their respective patients must have received an allo-HSCT, also be

able to speak/read English and be over 18. Caregiver exclusion criteria included history of psychiatric illness (caregiver report) in the past 18 months (unrelated to patient illness). This report examines those 140 caregivers (95% of consented population) at baseline who provided salivary cortisol samples and psychological variables of interest prior to randomization. Study procedures were approved by the Colorado Multi-Institutional Review Board and all participants provided informed consent.

Salivary Cortisol

Saliva samples were collected for 3 consecutive days using filter paper collection techniques as previously described [18] at 4 time points/day: awakening, 30 minutes following awakening, prior to lunch and 4PM. For ICV and slope calculations, the collection at 30 minutes after awakening was eliminated, to eliminate the cortisol awakening response (CAR) representing a different physiological response system [19] .

Psychological Measures

All participants completed a battery of questionnaires anchored to the past four weeks. These were completed around the time of saliva collection.

Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI)[20] is a well validated measure of sleep quality that provides sleep latency, sleep efficiency, and sleep duration. Scores 5 indicate sleep difficulty.

Mental Health Summary Score

To create a caregiver composite of mental health (CG-MH), we used principal component analysis (PCA) to evaluate and verify the shared variance of 6 affective variables (all with excellent independent reliability) at baseline. The measures examined for the PCA were as follows: Perceived Stress Scale [21], Center for Epidemiological Studies of Depression[22], Profile of Mood States[23], State Anxiety Inventory [24], the Impact of Events Scale [25] and the Short Form (SF-36) Health Survey Version 2, Mental Health Component [26] (SF-36 MH). As recommended by others[27], we required a stringent factor score of 0.70 or greater for inclusion in the composite. Our resulting Caregiver Mental Health Composite score differs from a PCA on 5 of these variables (dubbed Caregiver Distress score) previously reported [17, 28].

Analytic Approach

Cortisol data were log transformed to normalize their distribution prior to all calculations. For the ICV calculation, the cortisol level approximately 30 minutes after awakening was eliminated to model individuals' cortisol as a linear time trend from awakening to 4 PM [18]. For samples with missing collection times (20.6%), group means for the recorded collection time was imputed similar to prior approaches[14]. Since the slope of diurnal decline in cortisol is related to important clinical outcomes [11, 12], we estimated residuals (e_{ij}) from the following: $Y_{ij} = b_0 + u_{0i} + (b_1 + u_{1i})X_{ij} + e_{ij}$. Each individual's (i) average linear trend was modeled on cortisol's (Y_{ij}) linear relationship to recorded time of collection

(X_{ij} on a 24 hour clock) with a linear mixed model specifying intercepts and slopes as stochastic parameters, i.e. allowing them to vary by individual an amount u_{0i} from the intercept b_0 and an amount u_{1i} from the slope. We have observed reliable time registration by individuals in this age group using our unique collection devices [18]. Similar to previously published analyses [14], the standard deviation of each individual's residual from their model was then saved as a new variable of intraindividual cortisol variability (ICV). ICV data displayed adequate characteristics of normality (nonsignificant Shapiro-Wilkes test; low skewness and kurtosis statistics) prior to analyses. Additional cortisol characterizations included the diurnal slope (average cortisol values across the three days of collection are regressed on time of collection [29]), area under the curve (AUC; cortisol level from 4 times of collection computed via trapezoidal formula and averaged across days with respect to ground [30, 31]) and CAR (change in cortisol from awakening to 30 min after averaged across the three days of collection [19]). Each of these four cortisol representations was regressed on the psychological variables of interest (PSQI, CG-MH) after controlling for age[32] and sex[33], which have been shown to significantly affect daily circadian rhythm of cortisol[34] and have been applied as covariates in other studies of physiological variability (cardiovascular lability; [35]).

Results

Of the caregivers consented ($N = 148$), 140 provided sufficient cortisol samples¹ to fit the mixed model applied and are included in the current analysis. Caregivers were predominately white (91.4%), females (76%) with a mean age of 53 ($SD = 12.1$ years) and largely college educated (31% with college degree; 25% reporting completing some college). Caregivers were predominantly (71%) spousal caregivers. Further, this sample was relatively healthy, with an average rating of their own health as 4.2 ($SD = .68$) (scale of 1 to 5, with 1 being "poor" and 5 being "excellent"), an average Charlson Comorbidity Index of .24 ($SD = .56$), reporting an average consumption of .7 ($SD = 1.12$) drinks per day, 14% ($N = 19$) identified themselves as smokers, 59% ($N = 83$) engaged in regular exercise (60% reporting aerobic exercise at least once a week) and their average BMI was 27.89 ($SD = 5.61$).

PCA identified one common factor explaining 79.29% of the variance in the following variables with factor loadings greater than our criterion of .70: Perceived Stress Scale, Center for Epidemiological Studies of Depression, Profile of Mood States, State Anxiety Inventory, and the SF-36 MH)². This common factor (termed CG-MH) was coded such that higher scores indicated *poorer* mental health. CG-MH differs from a previously reported PCA (dubbed Caregiver Distress score), which included the Impact of Events scale, and not SF-36 MH [17, 28]. Correlations among all psychological variables tested for the PCA, in addition to the primary cortisol outcome of interest, are included in Table S1, Supplemental Digital Content 1.

¹Only one participant provided less than the possible 9 samples per person (providing 6 samples across 3 days). Analyses were re-run excluding this participant and the relationships described below remained.

²Kaiser-Meyer-Olkin value = .90; Bartlett's test of sphericity ($\chi^2(10) = 507.82, p < .05$); This one factor solution was fit the data compared to the two factor solution which only explained 7.19% of the shared variance. Visual inspection of the scree plot confirmed the superiority of the one factor solution.

Caregivers of Allo-HSCT patients' intraindividual cortisol variability (ICV) was significantly related to CG-MH ($\beta = .25$; $p = .009$) after controlling for age and sex (Table 2). Sleep quality was not significantly related to ICV ($\beta = .16$; $p = .069$). Both relationships trended in the predicted direction such that greater ICV was related to poorer psychological functioning and thus provide convergent confirmation. For illustrative purposes, raw cortisol data together with the best fitting line representing the diurnal decline are plotted for 3 participants with the lowest mental health scores with low ICV and for 3 participants with the highest mental health scores showing high ICV in Figure 1. Neither CG-MH nor sleep quality were significantly related to cortisol slope, AUC with respect to ground or CAR. All correlations among cortisol outcomes and psychological variables are presented in Table 1, with regression results are presented in Table 2.

Discussion

Consistent with hypotheses, ICV was significantly related to our composite measure of mental health. This is particularly noteworthy for these caregivers, since other markers of HPA-axis dysregulation (cortisol slope, AUC, CAR) did not demonstrate significant relationships with the two markers of psychological distress in this study [28]. The current findings are congruent with previous findings in which greater depressive symptoms were significantly related to greater ICV, whereas cortisol slope was not significantly related [14]. Notably, recent work from our group was unable to detect differences in these cortisol parameters (CAR, AUC, and slope) in these caregivers compared to healthy controls [28]. These results suggest that ICV may characterize a subtle change in the regulation of the HPA-axis which is correlated with self-reported measures of psychological distress and, as such, may further represent a predictor of later physiological disruption. Follow up studies are presently underway investigating longer term relationships to physiological regulation in chronically distressed caregivers.

While long-term caregivers are stressed (1), most Allo-HSCT caregivers in the current study were beginning this process and had been pre-selected for good health as part of the transplant screening process (Laudenslager, 2014). If the current results are viewed from a framework of allostatic load [36], the negative consequences of psychological disturbance (e.g., mental health composite) may not have yet influenced HPA-axis markers such as slope, AUC, or CAR. However, given that greater ICV is observed in major depression [16], which may be conceptualized as prolonged psychological distress, it suggests that ICV may represent early HPA change associated with allostatic load in the present study. This interpretation is in line with the hypotheses put forth with other physiologic variability parameters, such as cardiovascular lability in which small "bursts" of data reveal robust relationships with individual predictors (cognitive aging [35]; and, in our analyses, caregiver mental health composite). Of course, this hypothesis cannot be tested in the current cross-sectional design; future work may benefit from examining ICV applying longitudinal approaches in combination with bursts of individual data, potentially revealing how mental health changes over time.

These results should be interpreted in light of their limitations. First, the study design was non-experimental, and as such, causal interpretations cannot be made. Second, although the

study design includes three days' data, only limited cortisol variance or fluctuation is captured across the 3 time points each day. Therefore, the residuals used to calculate the intraindividual variability may not accurately reflect the entire time trend seen in the diurnal cortisol variation *within* each day of collection. Finally, the participants from which data is drawn is fairly homogenous (primarily white female, albeit reflective of caregivers more generally), and any conclusions from this work may not be generalizable to other populations. Future work should strive to recruit more diverse participants, as well as examine ICV over time and relationships among ICV and health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

HPA	hypothalamic pituitary adrenal
ICV	intraindividual cortisol variability
Allo-HSCT	Allogeneic hematopoietic stress cell transplant
CAR	Cortisol Awakening Response
AUC	Area under the curve
HLM	Hierarchical Linear Modeling

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Figure 1.

The 3 participants with the highest mental health (MH) composite scores (suggesting poorest MH relative to rest of the sample) are compared with the 3 participants with the lowest MH composite scores (best relative MH). Individual regression lines are plotted with their actual cortisol values, demonstrating that the participants with the highest MH scores have more variable cortisol levels around that individual's regression line (higher ICV). Sensitivity analyses (in which analyses are re-run sequentially eliminating participants one-by-one) revealed that the significant relationships held after elimination of these participants, in addition to the next 2 additional participants with relative high and low MH scores. Despite these individual slopes appearing flatter for those participants with poorest MH, this relationship was not significant ($r = .041$; $p = .67$).

Table 1
Bivariate correlations among psychological variables of interest and cortisol outcomes

	1.	2.	3.	4.	5.	6.	7.
1. Age ($M=53$; $SD=12.1$)	-	-	-	-	-	-	-
2. Mental Health Composite Score ($M=0$; $SD=1$)	-.31**	-	-	-	-	-	-
3. PSQI ($M=11$; $SD=2.84$)	-.045	.51***	-	-	-	-	-
4. Cortisol Awakening Response ($M=.30$; $SD=.63$ (nmol/L)/mins))	.13	-.026	.079	-.054	-	-	-
5. Cortisol Slope ($M=-.12$; $SD=.14$ (nmol/L)/hour)) α	.066	.041	-.094	-.063	.38***	-	-
6. Area Under the Curve ($M=65.20$; $SD=112.31$ (nmol/L) * hour)) α	.005	-.14	-.12	.18	.086	.095	-
7. IGV ($M=.64$; $SD=.23$)	.044	.23**	.17*	-.23**	.07	.040	-.075

($N=140$).

 $p < .001$;

**
 $p < .01$;

*
 $p < .05$

M =Group mean; SD =Standard deviation;

α Transformation applied and used in all analyses, reported means based on raw (untransformed) values.

Table 2
Cortisol calculations regressed on psychological variables of interest, controlling for age and sex.

	Dependent Variable					
	Cortisol Awakening Response		Cortisol Slope [€]		Area Under the Curve [€]	
	β	Total R^2	β	Total R^2	β	Total R^2
1. Caregiver Mental Health Composite	.037	.025	.099	.051	-.15	.025
2. Sleep Quality	.09	.025	-.066	.037	-.11	.014

[®] $p<.10$;
* $p<.05$;
** $p<.01$;
 β =Standardized beta weight; R^2 =R squared (variance explained)
^x Reverse coded such that higher scores are indicative of worse functioning;
[€] Transformations were applied to ensure normality of variable; All regression equations were adjusted for age and sex.