Blunted Diurnal Cortisol Pattern Is Associated With Frailty: A Cross-sectional Study of 745 Participants Aged 65 to 90 Years

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Background: The role of neuroendocrine alterations in the etiology of frailty syndrome is still poorly understood. Hypothalamic-pituitary-adrenal axis dysregulation is a plausible candidate pathway contributing to frailty. Thus, we sought to examine the associations of diurnal cortisol secretion with frailty in older adults.

Methods: A cross-sectional analysis was conducted among 745 study participants (age 65–90 years, mean age 75.1 years) of the population-based KORA Age study. Associations between salivary cortisol measures at awakening (morning 1 [M1]), 30 minutes after awakening (M2), and evening (E) and frailty criteria were determined.

Results: Lower cortisol levels in the first morning sample (M1) ($P = 0.18$) and M2 ($P = 0.14$) and increased E levels ($P = 0.004$) were observed in prefrail (35.17%, n = 262) and frail (3.36%, n = 25) individuals, in a dose-response manner. Frailty was strongly associated with smaller ratios of morning to evening levels; M1 to E ratio ($P = 0.02$) and M2 to E ratio ($P = 0.003$). Higher evening cortisol levels were associated with a 24% increased risk of a prefrail state (odds ratio, 1.22; 95% confidence interval, 1.03–1.44). A smaller morning to evening ratio was associated with an increased risk of low grip strength (1.42, 1.09–1.86) and gait speed (1.31, 1.02–1.68).

Conclusion: Frailty status is associated with blunted cortisol reactivity as demonstrated by lower morning and higher evening salivary cortisol levels.

Frailty is a geriatric paradigm that is not disease-specific but represents systemic dysregulation and decline in functional health. It is characterized by unintentional weight loss, feeling of exhaustion and fatigue, physical inactivity, slow gait speed, and low grip strength (1). Frailty confers a high risk for adverse outcomes such as functional dependency, institutionalization, and increased risk of mortality (1). To date, little is known about the mechanisms leading to frailty. In a recent meta-analysis (2), a greater diurnal decline of the hypothalamic-pituitary-adrenal (HPA) axis was associated with better physical performance in later life. This was also reflected by the Whitehall II cohort, in which a flatter diurnal pattern was associated with poorer health outcomes in older adults (3). Thus, impaired neuroendocrine regulation with increased vulnerability to stressors is a potential contributor to physiologic dysregulation observed in frail states (4). Furthermore, altered diurnal cortisol pattern indicated by lower morning and high cortisol in the late evening (5) may contribute to the development of sarcopenia, which likely contributes to frailty (6).

Neuroendocrine alterations are thought to be involved

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Abbreviations: BMI, body mass index; CAR, cortisol awakening response; DCS, diurnal cortisol secretion; E, evening; HPA, hypothalamic-pituitary-adrenal; morning 1, M1.

in the etiology of frailty but have not been well-characterized in a large community-dwelling population. Therefore, we sought to examine the dynamics of diurnal cortisol secretion (DCS) in frail, prefrail, and healthy study participants. Variations in characteristics of the study population such as multimorbidity (7), age, sex, smoking, body mass index (BMI) (8), and medications (9) affect cortisol levels and thus were considered as confounders in the association investigated between frailty and DCS. In particular, we tested the following hypotheses: (i) frailty criteria are associated with DCS and (ii) less variance of DCS is associated with frailty due to impaired neuroendocrine regulation.

Materials and Methods

Study setting and population

The KORA Age study was conducted between October 2008 and February 2009 and was approved by the Ethics Committee of the Bavarian Medical Association. All participants, aged more than 65 years, were selected from the previous surveys (Survey 1–4, conducted between 1984 and 2001) with participation rates ranging from 67% to 79% (10). For the current analysis, a standardized interview and medical examination were administered to 1079 study participants by trained medical staff, and only participants who provided complete, plausible salivary samples were included (n = 722, saliva sampling rate of 27%; see Supplemental Table 1, published on The Endocrine Society's Journals Online website at http://jcem.endojournals.org). Thus, 382 males and 363 females (age 65–90, mean age 75.1 years) were included in the analysis. In a dropout analysis of the excluded participants, no significant age and sex differences were observed (data not shown).

Salivary cortisol

Participants were individually instructed about the saliva sampling procedure and provided with additional detailed written information (Salivette salivary sampling test kit). Three saliva samples were assessed; in the morning after awakening (morning 1 [M1]), 30 minutes after awakening (M2), and in the late evening before bedtime (E). Cortisol levels were determined in duplicate using the Luminescence Immunoassay RE62011 (range 0.1–40 ng/mL, IBL) and the Victor Multilabel Plate Reader (PerkinElmer).

Frailty assessment

Participants were classified as frail if 3 or more of the following criteria proposed by Fried et al (1) were met, prefrail if 1 or 2 criteria were fulfilled, and nonfrail if none of the criteria applied: weight loss, loss of more than 5 kg in the past 6 months; exhaustion, a lack of feeling energetic and active over the last 2 weeks; physical inactivity, not performing any sports during summer and winter and walking less than 30 minutes daily; low walking speed, consuming the most time in the Timed Up and Go-Test (11) (in the highest quintile stratified according to sex and mean standing height); and weakness, lowest quintile (stratified according to sex and BMI) of the mean value of 3 grip strength measurements as determined using the JAMAR handheld dynamometer (Saehan Corp).

Covariates

Sociodemographic variables included age, sex and education. Low education was defined as less than 8 years of education. BMI was recorded as body weight in kilograms divided by the square meters of height. Someone who smoked cigarettes regularly or irregularly was considered as a current smoker. Multimorbidity was defined as the co-occurrence of more than two disease conditions on the Charlson Comorbidity Index (12).

Statistical analysis

Baseline descriptive analyses of demographic and clinical characteristics were stratified by frailty status. In case of nonnormality, tests were performed on log-transformed variables and results are presented as geometric means with antilog of SEs of the adjusted log means. Cortisol awakening response (CAR = M2 − M1) and the ratios of M1 to E (M1/E) and M2 to E (M2/E) were calculated. Least-squares means of cortisol measurements were calculated in age- and sex-adjusted models. Adjusted means with 95% CI are presented, and differences between groups were tested with general linear model procedures.

Multivariate linear regression models were used to assess the association of frailty and DCS (M1, M2, E, M1/E, and M2/E). All covariates and cortisol measures were entered into a multinomial logistic regression model with the outcome frailty to distinguish the risk of being frail or prefrail (as opposed to nonfrail) and then entered into a logistic linear regression with the outcome of each specific frailty criteria. Estimates from multinomial logistic regression analyses are expressed as increased risk per 1 SD of the respective cortisol measures.

Analyses were performed using SAS statistical software version 9.2 (SAS Institute) and P values $< .05$ were considered statistically significant. The STROBE (strengthening the reporting of observational studies in epidemiology) checklist was applied in preparation of the manuscript.

Results

Smaller M1/E ($P = 0.02$) and M2/E ($P = 0.003$) ratios were associated with frailty status in this present study. The commonly used CAR was not significantly different between the frailty categories. Compared with healthy individuals, frail (n = 25, 3.4%) and prefrail (262, 35.2%) individuals had lower mean of M1 ($P = .18$) and M2 ($P = .14$) and higher E ($P = 0.003$) cortisol levels (Table 1).

The associations of cortisol means (least-squares means adjusted by age and sex) with the 5 frailty criteria revealed that increased evening levels ($P = .002$) were observed in participants with slow gait speed, whereas lower morning levels ($P = .035$) were found in participants with low grip strength (Figure 1). In fully adjusted multinomial logistic regression models calculated for each of the 5 individual frailty criteria as outcome, an increased risk of low gait speed was associated with increasing evening cortisol level (1.35, 1.10–1.65, per 1-SD increase, $P = .004$) as well as

Table 1. Geometric Mean Concentration (Antilog of SE) of Various Cortisol Measures by Frailty States (n = 745)

Cortisol Measurement	Cortisol Concentration, ng/mL			
	Frail (25, 3.36%)	Prefrail (262, 35.17%)	Nonfrail (458, 61.48%)	*P* Value for Differences Between Groups[a]
M1	3.5 (2.4)	3.7 (1.8)	3.9 (1.8)	0.18
M2	4.2 (1.7)	4.8 (1.8)	5.2 (1.9)	0.14
E	0.9 (1.8)	0.8 (2.1)	0.7 (1.9)	0.004
CAR	1.2 (3.2)	1.17 (2.7)	1.4 (3.1)	0.17
M1/E ratio	5.2 (3.6)	6.72 (7.9)	7.9 (6.5)	0.02
M2/E ratio	6.6 (5.6)	8.52 (7.1)	10.5 (8.3)	0.003

[a] Adjusted for age and sex.

the ratio M2/E (1.42, 1.09–1.86, $P = .01$). A 51% increased risk of low physical activity was associated with an increase in CAR (1.51, 1.14–2.01, $P = .004$), and risk of low grip strength was associated with both ratios of M1/E (1.36, 1.03–1.79, $P = .03$) and M2/E (1.31, 1.02–1.68, $P = .04$). However, the association with both ratios was no longer significant if Bonferroni correction for multiple testing was applied (0.05/6, $P < .008$).

When the frailty construct was modeled in fully adjusted analyses, only increases in evening cortisol were associated with a 22% increased risk of prefrail vs healthy status (odds ratio, 1.22; 95% confidence interval, 1.03–1.44; $P = .02$). For the risk of being frail vs nonfrail, similar effects were observed, but results failed to show significance possibly due to the small number of frail participants (1.24, 0.83–1.83, $P = .3$). A sensitivity analysis with additional adjustment for chronic obstructive pulmonary disease, rheumatoid arthritis, and gastrointestinal disorders, which are associated with the use of glucocorticoid medications, did not alter the observed results (data not shown).

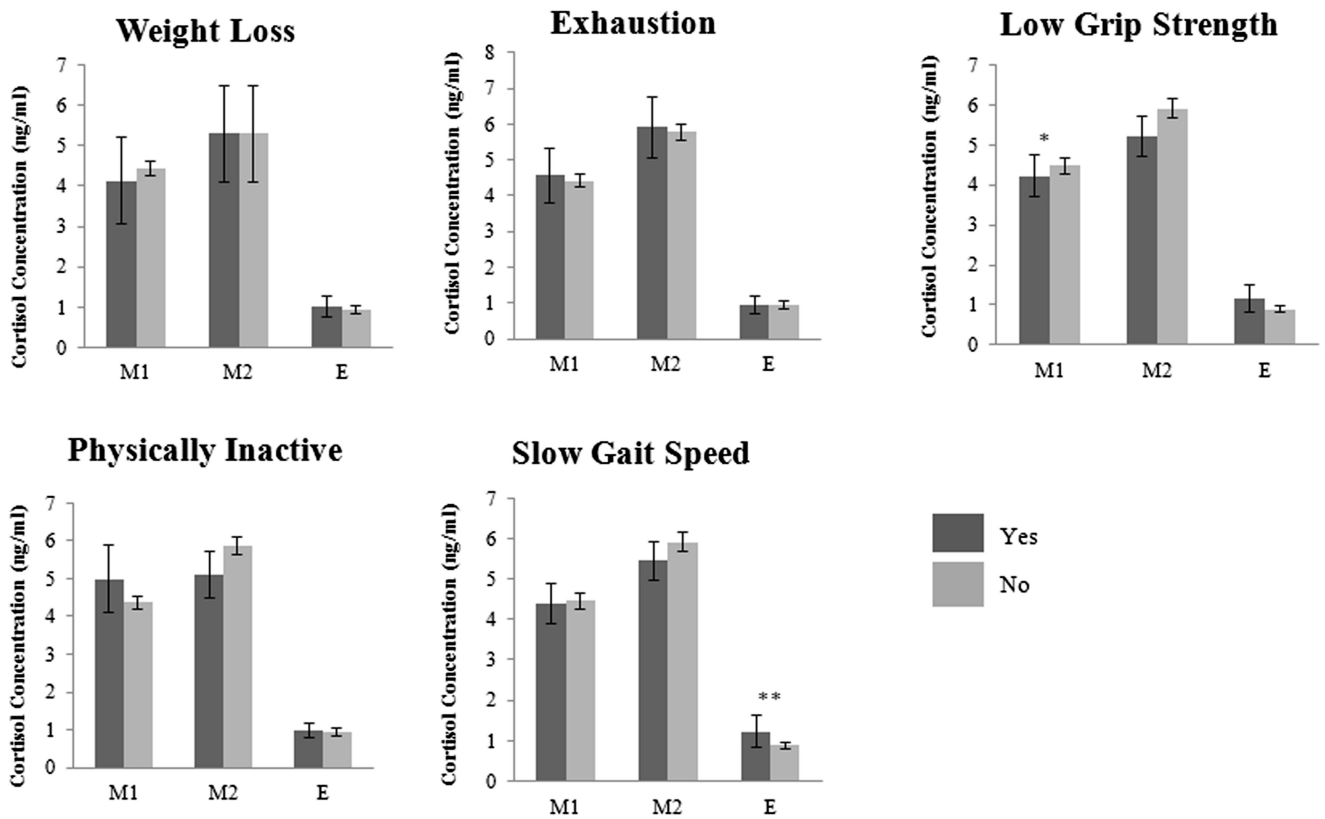

Figure 1. Adjusted geometric means of cortisol by frailty criteria.

Discussion

This study is the first to show evidence of a dysregulated DCS that features lower morning and higher evening cortisol levels in frail and prefrail elderly men and women from a large, community-based epidemiologic sample. This confirms the hypothesis that blunted cortisol levels (low reactivity) are associated with negative health outcomes (13). To the best of our knowledge, to date, only 2 studies have investigated this issue, among women (4) and in institutionalized elderly (14). In the first study, a smaller diurnal decline and higher evening cortisol were seen in women with greater frailty burden, whereas the second study reported higher cortisol values in both morning and evening samples from frail institutionalized elderly. Thus, our findings not only corroborate the results from the study among women but also expand the view that blunted diurnal cortisol responses were observed in both men and women with increasing frailty burden. Furthermore, the significance of the novel morning to evening cortisol ratios demonstrated in our study were likely influenced by the evening levels. This was recently demonstrated by a prospective study by Gardner et al (15), in which a higher evening cortisol level, which in turn contributed to less diurnal variability, predicted poorer physical performance in participants of the Caerphilly Study.

The dynamic regulation of DCS, indicating an individual's ability to adjust from the highest cortisol level in the morning to the lowest basal level at night, is clearly captured in the novel ratio concept introduced in this analysis. This ratio concept sharpens the current knowledge on the characteristics of DCS with flat or steep diurnal cortisol slope, CAR, and single morning or evening cortisol measurements. A smaller ratio (low morning and high evening levels) indicates a disrupted diurnal rhythm and is also comparable to a flatter diurnal pattern, which was observed in the older individuals of the Whitehall II cohort (3). The combination of morning to evening levels as a ratio appears to provide a better insight of diurnal cortisol rhythmicity and thus HPA axis reactivity. This supports the current hypothesis that a more dynamic HPA axis, rather than absolute cortisol levels per se, is more important in determining frailty status (2).

Among the 5 frailty criteria, grip strength and gait speed were significantly associated with altered morning to evening cortisol ratio but not weight loss, physical inactivity, and exhaustion. These results suggest a link of disrupted cortisol regulation and sarcopenia as the underlying pathophysiology of frailty (6). Our observations support the predominant role of muscle atrophy, reflected in the grip strength and gait speed criteria, and cortisol dysregulation in prefrail states. These results complement a recent meta-analysis that demonstrated associations between greater diurnal decline and gait speed (2). The clinical relevance of these findings is paramount because exercise and protein intake, which preserve and increase muscle mass, are successful first-line interventions for prefrail states (6). Furthermore, assessing frailty status in clinical settings may help in decision making for suitable patient-specific treatment (ie, invasive, conservative, or palliative care) because current disease-specific prognostic scoring systems are unable to differentiate between frail and nonfrail elderly (16). In a clinical setting, an assessment of frailty may be considered as time-consuming, and therefore, measurements of cortisol may offer a feasible alternative.

Study strengths and limitations

The strength of our study rests in the salivary sample collection from a large, sex-equivalent, representative population with a high study response rate. A disadvantage of this study is the low percentage (3.4%, n = 25) of frail elderly that were assessed. However, a wide range of prevalences have been reported in the literature (8%–59.1%) with lower prevalence observed using a physical frailty construct compared with a broader definition of frailty (2). We therefore cannot rule out a selection bias in this study, because only participants who were healthy enough could be assessed for gait speed. The easy and noninvasive salivary cortisol sampling method captures the DCS. Although the strictest quality control measures were taken, salivary sampling collection time deviance could be a potential source of variance adherent in the CAR measurement (17). Because the nature of cross-sectional studies cannot infer causality, a prospective analysis of the study population is warranted.

Conclusion

A blunted cortisol response of lower morning and higher evening cortisol levels reflects the altered HPA axis reactivity that contributes to the underlying pathophysiologic mechanisms leading to frailty. The novel morning to evening cortisol ratio identifies muscle atrophy as a prominent marker of prefrail individuals, a vulnerable patient population that would likely benefit from targeted interventions.

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