



## Temporal relationships between awakening cortisol and psychosocial variables in inpatients with anorexia nervosa – A time series approach



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### ABSTRACT

**Objective:** The aim of the study was to investigate the characteristics of the awakening salivary cortisol in patients with anorexia nervosa (AN) using a time series design. We included ten AN inpatients, six with a very low BMI (high symptom severity, HSS group) and four patients with less severe symptoms (low symptom severity, LSS group).

**Methods:** Patients collected salivary cortisol daily upon awakening. The number of collected saliva samples varied across patients between  $n = 65$  and  $n = 229$  (due to the different lengths of their inpatient stay). In addition, before retiring, the patients answered questions daily on the handheld regarding disorder-related psychosocial variables. The analysis of cortisol and diary data was conducted by using a time series approach.

**Results:** Time series showed that the awakening cortisol of the AN patients was elevated as compared to a control group. Cortisol measurements of patients with LSS essentially fluctuated in a stationary manner around a constant mean. The series of patients with HSS were generally less stable; four HSS patients showed a non-stationary cortisol awakening series. Antipsychotic medication did not change awakening cortisol in a specific way. The lagged dependencies between cortisol and depressive feelings became significant for four patients. Here, higher cortisol values were temporally associated with higher values of depressive feelings.

**Conclusions:** Upon awakening, the cortisol of all AN patients was in the standard range but elevated as compared to healthy controls. Patients with HSS appeared to show less stable awakening cortisol time series compared to patients with LSS.

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### 1. Introduction

Anorexia nervosa (AN) is a serious eating disorder leading to high morbidity and mortality as a result of both malnutrition and suicide (Zipfel et al., 2000). For many years the hypothalamic-pituitary-adrenal (HPA) axis activity and its correlates have been extensively investigated leading to the assumption that hypercortisolism would be present in the majority of underweight AN patients (Licinio et al., 1996; LoSauro et al., 2008).

Salivary measurements of cortisol are used as biomarkers of stress (Kudielka et al., 2012). Some authors suggested that hypercortisolism is a direct consequence of undernutrition in patients with AN. It was further assumed that functional changes in the HPA axis of AN patients would be reversed upon weight restoration (Gold et al., 1986;

Södersten et al., 2006). However, in several studies it was difficult to distinguish whether the HPA axis abnormalities were related to starvation or to the disorder itself (LoSauro et al., 2008). The cross-sectional design of previous studies did not allow one to draw corresponding conclusions: the cortisol of AN patients typically was measured once, twice (pre and post-treatment), or several times over the course of a day to either capture the cortisol awakening response (CAR) and diurnal profile or to assess a stress response (Monteleone et al., 2011a; Shibuya et al., 2011). However, cortisol levels are not only strongly influenced by the time of day but also by situational factors (Adam et al., 2006). In order to capture the individual dynamics of emotional, behavioral, and endocrine factors in AN, more frequent assessments over a longer time period would be valuable.

In general, in psychosomatic research inferences about relationships between variables are frequently obtained by comparing aggregated data from groups of individuals (Barlow and Nock, 2009). However, these inferences are often not valid for the individual patient. An alternative to the common study designs offers the idiographic approach which focuses on the intensive study of individuals over time

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(Rosmalen et al., 2012). Here, analyses are performed for single individuals based on many repeated measurements. Advantages of the idiographic research strategy are the flexibility and the possibility to detect differences between individuals and to appropriately model temporal relationships between variables (Molenaar and Campbell, 2009). Cortisol shows typically large fluctuations over time within individuals (Rosmalen et al., 2012). We therefore believe that an idiographic approach with a long-term repeated measurements design could be ideally suited to adequately capture the cortisol activity of patients and to determine temporal relationships between cortisol and psychosocial variables.

To date, no study has closer described the characteristics of the awakening cortisol in AN patients. However, a few studies have investigated the CAR which in its significance has to be differentiated from the awakening cortisol (Monteleone et al., 2011b; Oskis et al., 2012). Monteleone et al. (2011b) reported that in eight adult AN patients from the restrictive subtype the salivary cortisol at awakening was significantly enhanced compared to eight age-matched healthy women. In a more recent study, Monteleone et al. (2014) found that, compared to healthy controls, adult AN patients exhibited an enhanced CAR. However, here, the authors did not state explicitly whether the differences in cortisol level were found in the awakening or the post-awakening measurements. In one of our own recent studies we could show that in AN patients with a high disorder severity (HSS), the CAR was significantly lower compared to patients with a low disorder severity (LSS) (Wild et al., 2014). Here, the two groups did not differ regarding the awakening cortisol but did differ in regard to the post-awakening levels.

In the present study, we implemented a longitudinal - time series design - to more closely investigate the characteristics of the awakening cortisol and its associations to disorder severity and psychosocial variables in AN patients. The aim of the study was (a) to investigate the characteristics of the awakening salivary cortisol in patients with AN, and (b) to determine the temporal relationships between awakening cortisol, disorder severity, and psychosocial variables. The study was explorative. However, we hypothesized that in most AN patients, the majority of the awakening cortisol values would be enhanced compared to a control group. We also hypothesized that the time series of awakening cortisol would be distinguishable between patients with HSS and patients with LSS. However, the nature of the differences between time series was - due to the lack of similar studies - not predictable.

## 2. Material and methods

### 2.1. Design

The study was approved by the local ethics committee of the Medical University Hospital, Heidelberg. Patients were informed about the study and written informed consent was obtained. In total, 12 women with anorexia nervosa were enrolled.

At the beginning of the study the Structured Clinical Interview for DSM-IV (SCID) was conducted (Wittchen et al., 1997); all patients met the diagnostic criteria for AN.

During the study period, the patients collected salivary cortisol daily at awakening and answered several questions on a handheld computer (electronic diary) regarding their condition at the time of salivary collection. In addition, the patients answered questions daily before going to sleep on the handheld computer regarding disorder-related psychosocial variables.

Out of the 12 recruited patients, we had to exclude two patients because their number of repeated measurements (time series) was too short due to their short inpatient stay.

### 2.2. Study sample

The 10 included female AN patients were admitted to two different wards of the Department of General Internal Medicine and

Psychosomatics at the University Hospital Heidelberg. They were part of a larger study sample that we investigated regarding the characteristics of the cortisol awakening response (CAR) (Wild et al., 2014). However, due to limited resources the more detailed measurement and analysis of cortisol time series was restricted to a subsample.

Six patients were recruited from an integrated working psychosomatic and internal-medicine ward (a group with high symptom severity, HSS). This ward is specialized in the treatment of AN patients with a very low BMI (BMI < 12). It provides an intensive therapeutic program in a safe environment that includes supervised and guided meal intake and supports weight management. The other four patients were recruited from a psychotherapeutic ward (a group with low symptom severity, LSS). This ward provides a specialized multimodal psychodynamic-orientated treatment program for eating-disordered patients. The differing indications for the admission to the two wards depend on the severity and chronicity of the illness. Patients with a BMI below 15 kg/m<sup>2</sup>, and patients with either a chronic course of the disease or those who had suffered several relapses that required inpatient treatment are preferentially admitted to the integrated working psychosomatic and internal medicine ward.

The characteristics of the 10 included AN patients are shown in Table 1.

A short description of the disorder history and treatment course of each patient is given in Appendix A.

To compare the awakening cortisol values from the AN patients with a control group we used data from another study including salivary cortisol measurements from 26 healthy women. In the control group, the awakening cortisol was measured on two consecutive days using the same instructions as for the AN patients. The healthy controls had a mean age of 21.8 years (range: 19–27) and a mean BMI of 21.4 kg/m<sup>2</sup> (STD = 1.7).

### 2.3. Cortisol measurements

Throughout the course of the inpatient treatment, saliva samples were collected daily upon awakening. The patients were instructed to take saliva samples immediately upon awakening and before brushing their teeth. On both wards the predefined morning “rising time” was 7:00 a.m. However, awakening-time varied both across patients and days. We therefore clearly instructed the patients to provide the first saliva sample upon awakening (and not at a predefined time point). The exact times of the daily saliva collection were recorded. The number of collected saliva samples varied across patients between  $n = 65$  and  $n = 229$  (due to the different lengths of their inpatient stay).

At the same time as saliva collection, patients completed daily on a handheld computer five questions regarding the quality of sleep the previous night, perceived current stress, current depressive feelings, anticipated nervousness, and positive anticipations for the day.

**Table 1**  
Characteristics of the patients.

		HSS group	LSS group
		N = 6	N = 4
Age	Mean (SD)	23.2 (4.4)	25.3 (4.5)
	Range	19–30	23–32
Duration of illness (years)	Mean (SD)	7.5 (7.1)	2.8 (1.3)
	Range	1–20	1–4
BMI (at beginning of study)	Mean (SD)	12.8 (1.6)	15.6 (0.9)
	Range	11.2–14.8	14.3–16.2
BMI (at end of study)	Mean (SD)	17.0 (1.7)	16.6 (0.5)
	Range	15.1–19.0	16.2–17.3
Subtype: restrictive	N (%)	5 (83)	4 (100)
Duration of stay (no. of days)	Mean (SD)	169.3 (59.5)	82.8 (1.5)
	Range	98–250	82–85

HSS = high symptom severity, LSS = low symptom severity.

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