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The relationship between diurnal cortisol secretion and climacteric-related symptoms

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ABSTRACT

Objectives: Chronic stress, also associated with climacteric-related symptoms, may influence cortisol secretion. We studied cortisol metabolism in peri- and postmenopausal women with diverse climacteric-related symptoms.
Study design and main outcome measures: The study population was 35 women, aged 45–70 years. Plasma cortisol levels were measured from blood samples collected every 20 min over 24 h. Urinary cortisol was analysed from 24-hour urine collections. Climacteric-related symptoms (vasomotor, sleep, depressive, anxiety, cognitive, sexual, menstrual, and somatic) were evaluated with the Women's Health Questionnaire (WHQ). Associations between cortisol variables (24-hour, night, day, maximum, minimum, morning baseline, cortisol awakening response (CAR), area under the curve, slope, and 24-hour urinary cortisol) and the symptoms were first examined with a correlation analysis. Then, the women were divided into two groups according to their climacteric symptomatology, and differences in cortisol variables between the groups were investigated. Diurnal cortisol curves by symptomatology were also analyzed visually.
Results: In the correlation analysis, more frequent vasomotor symptoms were associated with a higher CAR (r_s = 0.37, p = 0.039) and lower 24-hour urinary cortisol excretion (r_s = -0.45, p = 0.012), and more frequent depressive symptoms were associated with a higher minimum cortisol level (r_s = 0.33, p = 0.0498). When the women were divided into two groups, women with more frequent vasomotor (p = 0.012) or somatic symptoms (p = 0.021) had a lower 24-hour urinary cortisol excretion than less symptomatic women.
Conclusions: Although previous studies have reported associations between climacteric-related symptoms and cortisol secretion, these two factors were not substantially interrelated in our study.

1. Introduction

Blood cortisol levels are regulated by the hypothalamic pituitary adrenal (HPA) axis [1,2], which is affected by not only physical but also psychological stress [2,3]. Acute stress, both physiological and psychological, leads to a rapid increase in cortisol secretion [2,3], while chronic stress can trigger either an increase or a decrease in cortisol levels [2,3]. However, to understand the influence of stress on cortisol metabolism, it is valuable to investigate changes in the diurnal variation in cortisol levels, especially an increase or decrease in the cortisol awakening response (CAR) – a sharp peak in cortisol levels after awakening [1,4,5] – and a flattening of the general decline from morning to evening [1].

Cortisol levels increase with age [6,7], and this increase is more pronounced in women than in men [6]. Moreover, there is some evidence that in women cortisol levels are higher during the late stage of the menopausal transition and then return to the previous level as women reach a postmenopausal state [8]. In addition to the gender differences in age-related changes in cortisol levels, cortisol responses to stress may be weaker in women than in men [9].

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Previous studies evaluating the relationship between cortisol levels and climacteric-related symptoms have produced varying and conflicting results [8,10–20]. More frequent vasomotor symptoms (VMS) have been associated with a higher CAR [13], a lower cortisol level after awakening [11], a higher early afternoon level [11], a flatter diurnal cortisol slope [12], higher daytime [16] and lower overnight urinary cortisol excretion [14], and higher hair cortisol levels [12]. Sleep disturbances and mental symptoms have also been linked to alterations in cortisol metabolism [8,15,18,21–27]. However, most studies have not specifically addressed symptoms experienced during menopause but have instead included both genders or various age groups [21–27]. Studies in midlife women have evaluated relatively few cortisol variables. In a large US study, the Seattle Midlife Women's Health Study (SMWHS), sleep problems were associated with lower overnight urinary cortisol [15], but depressive symptoms [20] or cognitive difficulties [19] were not. In another large US study, the Study of Women's Health Across the Nation (SWAN), more frequent depressive symptoms and anxiety were associated with a flatter salivary cortisol slope, but not with mean salivary cortisol levels [17]. In an Italian study of 85 women, more frequent depressive symptoms and anxiety were both associated with higher 24-hour urinary cortisol [16].

Our aim was to investigate associations between cortisol levels and metabolism and certain symptoms commonly linked with menopause. Since changes in the diurnal cortisol profile have been shown to be crucial [1], we quantified plasma cortisol levels every 20 min for 24 h. To evaluate levels of free cortisol, 24-hour urine samples were collected. We hypothesized that climacteric-related symptoms would be associated with cortisol secretion: variation in cortisol secretion may produce physical or psychological symptoms suggestive of climacteric-related symptoms, and climacteric-related symptoms may induce a stress-like condition that affects cortisol production.

2. Methods

2.1. Participants

Thirty-five women were recruited. The present study was a substudy for a larger investigation of the effects of menopause and hormone therapy (HT) on sleep and cognitive functions. Women were defined as premenopausal or perimenopausal if they had an ongoing regular or irregular menstrual cycle (with the exception of one hysterectomized woman) and a serum follicle stimulating hormone (FSH) level < 23 IU/ml. The postmenopausal state was defined by age (58 years or older) and chronic amenorrhea. Of the women, 17 were either premenopausal or perimenopausal (later referred as perimenopausal) and 18 were postmenopausal. The mean age of the perimenopausal women was 47.9 years (standard deviation [SD] 1.7, range: 45–51 years), and the mean age of the postmenopausal women was 62.8 years (SD 2.9, range: 58–70 years). Exclusion criteria included: malignancies, neurological, cardiovascular (except treated hypertension), endocrinological (except treated hyperlipidemia), and mental disorders; abuse of alcohol or drugs; smoking; excessive consumption of caffeine (more than five cups daily); and other conditions possibly affecting sleep (e.g., fibromyalgia or restless legs syndrome). The use of HT and medications affecting the central nervous system was not allowed; a washout time of three months was required. Full blood count (hemoglobin, leukocytes, thrombocytes) and serum thyroid stimulating hormone (TSH) concentration were within the female reference range, and a urine drug screen was negative in all participants. In the perimenopausal group, only one woman had used HT (for only three months and had discontinued HT 10 months before the study). In the postmenopausal group, 13 women had used HT (for a mean of 73.5 months, range 3–156 months, and average time since discontinuation of 48.6 months, range 10–144 months). To ensure that all women had a regular sleep-wake schedule (22:00–23:00 h to 06:00–07:00 h), they were required to complete sleep diaries three weeks before and one week after the cortisol sampling. The basic characteristics of the participants are shown in Table 1.

Table 1
Basic characteristics.

N	35
	Mean (SD, Range)
Age, years	55.2 (7.9, 45-70)
Body mass index, kg/m^2	26.0 (4.2, 20.6-38.1)
	N (%)
Marital status	
Single	3 (8.6)
Married, the first marriage	19 (54.3)
Re-married	3 (8.6)
Cohabiting	3 (8.6)
Divorced	5 (14.3)
Widowed	2 (5.7)
Employment	
Employed	18 (51.4)
Unemployed	14 (40.0)
Retired	3 (8.6)
Smoking	
Never	32 (91.4)
Yes	
Occasionally	2 (5.7)
Daily, fewer than 10	1 (2.9)
Daily, more than 10	0
Hysterectomized[a]	4 (11.4)
One side oophorectomized[b]	1 (2.9)
Both side oophorectomized[b]	1 (2.9)

[a] One of the hysterectomized women was perimenopausal and three were postmenopausal.
[b] Both oophorectomized women were postmenopausal.

2.2. Study design

The women spent three consecutive nights in the sleep laboratory at the Sleep Research Unit, Department of Physiology, University of Turku. The first night was for adaptation. During the second day, the 24-hour urine samples were collected to measure urinary cortisol excretion. In the evening, before the third night, an intravenous catheter was placed into the forearm at 19:00 h, and blood sampling started at 21:00 h. The samples were drawn every 20 min for 24 h, for a total of 73 blood samples per person. During the night (23:00 – 07:00 h), the catheter was connected to a plastic tube running through a soundproof lock into an adjoining room to allow repeated blood sampling with a minimal disturbance to sleep. The catheter was kept patent with a slow heparinized saline infusion. All-night polysomnography (PSG) was performed every study night. The women went to bed on the third evening (lights-off) at 23:00 h and were awakened (lights-on) at 07:00 h. PSG indicated that 19 women woke up before lights-on (05:15 – 06:59 h), but, in line with the study protocol, they stayed in bed until lights-on. Women were not allowed to exit the windowless sleeping room during the nighttime (23:00 – 07:00 h), and only red light was allowed for illumination overnight when necessary. There was a bucket toilet in the sleeping room. Five women urinated once and one woman twice during the night of urine collection. During the night of blood collection, three women urinated once and two women twice. None of the women had need to defecate during the night. For the study to which the women were originally recruited, cognitive tests were performed on the morning of the third and fourth days. The schedule and content of the days, including nutrition, were similar for each participant. Perimenopausal women were examined in their follicular phase.

The blood samples were drawn into Li-Heparin tubes, placed in the refrigerator (4 – 8 °C) for 20 min, centrifuged, and frozen immediately. Plasma cortisol levels were measured with AutoDELFIA assays (PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland).