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Burnout is associated with elevated prolactin levels in men but not in women

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ABSTRACT

Objective: Prolactin levels have been shown to be increased by different types of psychosocial stress. Since burnout is a consequence of long-term psychosocial stress, prolactin levels might also be affected in burnout. The aim of this study was to investigate whether there are differences in prolactin levels between individuals who report burnout and others.
Method: Morning fasting serum prolactin levels were compared between individuals who reported burnout (24 men and 25 women) and individuals who reported no burnout (25 men and 13 women). Women were tested in the follicular phase of the menstrual cycle. Men and women were analysed separately.
Results: Men who reported burnout exhibited significantly higher (34%) serum prolactin levels compared to men who reported no burnout. The prolactin levels in women who reported burnout were not different from the levels in the women who reported no burnout before or after adjusting for estradiol levels.
Conclusions: This study indicates that prolactin levels are higher in men with burnout than men without burnout but not affected in women with burnout. Why no association was seen in women needs to be further explored.

Introduction

Burnout has been defined as a negative affective state consisting of emotional exhaustion, cognitive weariness and physical fatigue, and is caused by chronic psychosocial stress [1]. Besides the mental health burden and consequences for quality of life, there is growing evidence that burnout can negatively influence physical health. Burnout has been associated with an increased risk of cardiovascular disease [1–4], type 2 diabetes [5], musculoskeletal disorders [6] and impaired fertility [7]. Adverse associations have been seen between burnout and several physiological parameters indicating dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [8–10]. Most research on the physiological effects of stressors deals with the catabolic reactions with measurement of cortisol and catecholamines, or effects on the cardiovascular system. The present study investigates burnout in relation to serum levels of prolactin.

Prolactin is a peptide hormone primary synthesized and secreted by the lactotrope cells in the anterior pituitary gland. The secretion of prolactin from the lactotrope cells is regulated by different hypothalamic releasing hormones; thyrotropin-releasing hormone (TRH) (among others) has a stimulatory effect on prolactin secretion while dopamine, which is the most important regulator of prolactin secretion, has an inhibiting effect [11]. Prolactin levels are enhanced by estradiol [12–14]. Accordingly, prolactin levels are higher in women than men and vary between women in different phases of the menstrual cycle, post-menopausal women and pregnant women [15,16]. Prolactin was given its name for its ability to promote lactation, but it is a multifunctional hormone, with over 300 biological activities including functions e.g. in the reproduction, metabolism, and the immune system [11]. Prolactin levels have been reported to be affected by different types of psychosocial stressors. Elevated prolactin levels have been reported in response to acute stressors such as acute psychosocial laboratory stress [17], parachute jumping [18], and skydiving [19]. Prolactin levels have also been seen to be elevated in more prolonged stress situations such as during academic examinations [20,21], reorganization at work [22,23], threat of unemployment [23], and in subway drivers who had been exposed to "person under train" experience [24] and in relation to high job strain [25,26]. Prolactin may thus also be affected in individuals reporting burnout symptoms, as a consequence of chronic psychosocial stress, but this has not been thoroughly studied. Particularly, knowledge on prolactin in relation to symptoms of burnout in men is missing since there is no publication available that has included men. Three publications that investigated prolactin levels in women with burnout were found and these reported no differences in prolactin levels between the subjects with burnout and the others [27–29]. Since estradiol level is an important factor for prolactin levels, conclusions are difficult to draw from these studies since the study groups consists of women in different phases or post-menopausal women (which

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are not compared) or information on menstrual phase are missing. The aim of this study was to investigate whether there are differences in prolactin levels between individuals that report high burnout scores (burnout group) and individuals that report low burnout scores (non-burnout group). The study included both men and women and the women were scheduled to be tested in the follicular phase of the menstrual cycle.

Method

Subjects

Originally, 200 otherwise healthy individuals (50% men) in the age of 25 to 50 years were available to be included in the present study. These 200 individuals were recruited from an ongoing longitudinal cohort study at the Institute of Stress Medicine in Gothenburg, Sweden and from advertisements in daily newspapers with the aim to find biological markers of psychological stress. Inclusion stratification was initially applied to ensure that participants varied in terms of degrees of perceived stress. Inclusion was therefore based on self-reported level of perceived stress using a single item question from the General Nordic Questionnaire for Psychosocial and Social Factors at Work (QPS Nordic) instrument [30] : "Stress means a situation in which a person feels tense, restless, nervous, or anxious, or is unable to sleep at night because his/her mind is troubled all the time. Do you currently feel this kind of stress?" The response was recorded on a five-point scale varying from "not at all" to "very much." To ensure that participants varied in terms of degrees of perceived stress, 40 participants (20 men, 20 women) were selected from each of the five stress categories to be included the initial sample of 200 individuals. Before inclusion, the subjects underwent a screening test, including anthropometric measurements and obtaining blood samples to ensure the following exclusion criteria; having a body mass index less than 18.5 kg/m^2 or over 30 kg/m^2, high blood pressure, infection, vitamin B-12 deficiency (high homocysteine), known systemic disease such as diabetes or thyroid disease or known psychiatric disease. Women taking estrogens, nursing, pregnant and postmenopausal women were not included. Subjects who were taking psychoactive medications or any medications that may affect the hypothalamus–pituitary–adrenal (HPA) axis function were not included. The inclusion and assessment period was spread across the year for all the different stress-groups. Therefore there were no general differences between the stress groups in terms of when (during which season) they were included and assessed. Among the initial 200 participants, 199 individuals (100 men; 99 women) had data regarding burnout (see burnout scoring). Of these 199 individuals, blood samples had been collected from 198 individuals (100 men; 98 women). For female subjects, the blood samples were collected at a day during the 5 to 10 day of the menstrual cycle (self-reported follicular phase). Menstrual cycle phase was then validated by measuring serum levels of estradiol and progesterone. Of the 98 women, 7 women had missing data on estradiol and progesterone, and thus 91 women had all data required (burnout score, prolactin, estradiol and progesterone). One woman had extremely low estradiol level, indicating oophorohysterectomy, and was accordingly excluded. The results confirmed that 67 of the remaining 90 females were really tested in the follicular phase while 23 of the females were not. These 23 women were excluded. Among these 100 men and 67 women, the individuals with burnout scores above 3.75 (cut-off value for burnout) were considered as burnout subjects (24 men; 25 women) and individuals with burnout scores lower than 2.0 (which is considered as clearly no burnout) were considered as non-burnout subjects (25 men; 13 women) and included in the present study. 80 subjects (51 men and 29 women) had scores higher than 2 but lower than 3.75. The study was approved by the Regional Ethical Review Board in Göteborg, Sweden, and was conducted according to the Helsinki Declaration. All participants gave written informed consent before entering the study.

Physiological measurements

Blood samples were drawn in the morning between 7.30 and 10 from an antecubital vein. The subjects had fasted overnight. The samples were centrifuged (serum was separated from plasma) and stored at −80 °C until assayed. Serum concentrations of prolactin were measured by immunochemiluminometric assay (limit of detection, 0.6 μg/L) (Abbott Laboratories, Diagnostic Division, Abbott Park, IL, USA). Estradiol and progesterone was measured by liquid chromatography tandem mass spectrometry (LC–MS/MS). Inter-assay coefficients of variation were below 6% for prolactin and below 10% for estradiol and progesterone. Just before blood sampling, anthropometry measurement was performed.

Psychological measurements

Burnout was measured with the Shirom-Melamed Burnout Questionnaire (SMBQ) [1]. SMBQ contains 22 items (graded 1–7) which measuring the different aspects of burnout; emotional and physical exhaustion, tension, listlessness and cognitive weariness. A mean burnout index was calculated for each participant. The index can range from 1 to 7. Commonly used cut off value for high burnout is 3.75. As described above in the selection of participants section, individuals with mean burnout scores 3.75 and higher were classified as burnout subjects and individuals with mean burnout scores 2.0 and lower were classified as non-burnout subjects.

Statistical analysis

Prolactin and estradiol showed a non-normal distribution (checked by the Kolmogorov–Smirnov test) and was therefore log-transformed before statistical analysis. Pearson's correlation was computed among prolactin levels and possible predictors; age, BMI and estradiol levels (all subjects were included in these analyses). Spearman's rank correlation analysis was performed to analyse the relationship between prolactin levels and burnout scores. Strength of correlations were classified according to Cohen [31], which means that $r = 0.10$ to 0.29 or -0.10 to -0.29 were classified as small, $r = 0.30$ to 0.49 or $r = -0.30$ to -0.49 were classified as medium and $r = 0.50$ to 1.0 or $r = -0.50$–1.0 were classified as large strength of correlations. T-tests were performed to analyse possible differences in age, BMI, estradiol and prolactin levels between the burnout group (SMBQ $\geq$ 3.75) and the groups without burnout (SMBQ $\leq$ 2 and SMBQ = 2–3.74, respectively). ANCOVA was used to investigate differences in prolactin levels between the groups (only females) after adjusting for estradiol. All analyses were performed separately for men and women. For all tests, the level of significance was set at $p \leq 0.05$, two-tailed. The analyses were conducted with IBM Statistics 20 (SPSS Inc., Chicago, IL, USA).

Results

The subjects are described in Tables 1 and 2, men and women separately. As expected, the women had higher prolactin levels then the men (11.9 μg/L, 8.6 μg/L; respectively, $p < 0.001$). All participants except one had prolactin levels within the range considered as normal (reference values: 3.0–20 μg/L and 5.0–27 μg/L; men and women, respectively). One man who reported burnout had prolactin levels slightly above the normal range.

Prolactin levels in association with age, BMI and estradiol levels

Small to medium strengths of correlations were seen. Prolactin levels were negatively associated with age in men ($r = -0.35$, $p < 0.001$) but not in women ($r = 0.15$, $p = 0.224$). Prolactin levels were negatively associated with BMI in both men ($r = -0.22$, $p = 0.025$) and women ($r = -0.34$, $p = 0.005$). Prolactin levels were positively associated with estradiol levels in women ($r = 0.39$, $p = 0.001$) but not in men ($r = 0.05$, $p = 0.611$).

Prolactin levels in burnout subjects compared to non-burnout subjects

The men who reported burnout had higher prolactin levels than the men who reported no burnout ($p = 0.004$). The mean prolactin level in the burnout group was 34% higher