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Research paper

Relative hypocortisolism is associated with obesity and the metabolic syndrome in recurrent affective disorders

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ABSTRACT

Background: Cardiovascular disease (CVD) is one of the main causes of excess deaths in affective disorders. Affective disorders are associated with increased frequencies of CVD risk-factors such as obesity, dyslipidemia, and metabolic syndrome. Stress-induced chronic cortisol excess has been suggested to promote obesity and metabolic syndrome. Chronic stress with frequent or persisting hypothalamic-pituitary-adrenal-axis (HPA-axis) hyperactivity may, over time, lead to a state of low HPA-axis activity, also denoted hypocortisolism. A low-dose weight-adjusted dexamethasone-suppression-test (DST) is considered to be a sensitive measure of hypocortisolism.
Methods: 245 patients with recurrent depression or bipolar disorder and 258 controls participated in a low-dose DST and were also examined with regard to metabolic status.
Results: Patients with hypocortisolism (low post-DST cortisol) compared with patients without hypocortisolism (normal or high post-DST cortisol) exhibited increased odds ratios (OR) for obesity (OR=4.0), overweight (OR=4.0), large waist (OR=2.7), high LDL (OR=4.2), low HDL (OR=2.4), high LDL/HDL ratio (OR=3.3), high TC/HDL ratio (OR=3.4) and metabolic syndrome (OR=2.0). A similar pattern but less pronounced was also found in the control sample.
Limitations: The cross sectional study design and absence of analyses addressing lifestyle factors.
Conclusions: Our findings suggest that a substantial portion of the metabolic disorders and cardiovascular risk factors seen in recurrent affective disorders are found among individuals exhibiting hypocortisolism. This might indicate that long-term stress is a central contributor to metabolic abnormalities and CVD mortality in recurrent affective disorders.

1. Introduction

In recurrent affective disorders such as bipolar disorder and unipolar recurrent depression expected life span is significantly shorter than in the general population (Ajetunmobi et al., 2013; Walker et al., 2015). Recent studies have found that for patients with recurrent affective disorders the impact of somatic comorbidities equals or surpasses the effects of suicide on life expectancy (Ajetunmobi et al., 2013; Walker et al., 2015). Cardiovascular disease (CVD) is the main cause of excess deaths due to somatic comorbidities and affective patients have twice the mortality rate than the general population (Rugulies, 2002; Westman et al., 2013). Affective disorders are also associated with an increase in CVD risk factors such as obesity, dyslipidemia, and metabolic syndrome (McIntyre et al., 2009; Taylor and MacQueen, 2006). Although several life style factors such as smoking, unhealthy diet, and lack of physical activity as well as low socioeconomic status and the side effects of drugs may contribute to the increase in CVD risk factors and CVD, more research is needed that examines the fundamental biological link between affective disorders and CVD not mediated through the above mentioned factors (Taylor and MacQueen, 2006). Stress may be one possible link. In the general population, chronic stress has been estimated to account for a 1.5-fold excess risk of developing CVD (Steptoe and Kivimaki, 2013). One pathway between stress and CVD is believed to be the development of metabolic abnormalities (Steptoe and Kivimaki, 2013). Psychological and emotional distress has been proposed as a common starting point for weight gain and as the missing link between socioeconomic disadvantages and obesity (Hemmingsson, 2014). Chronic stress results in frequent and persisting activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal-axis (HPA-axis). HPA-axis activation

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leads to cortisol excess. Cortisol is known to increase visceral fat accumulation as well as blood pressure and blood glucose. Chronic cortisol excess has therefore been suggested as the mechanism behind stress-induced metabolic changes and obesity (Rosmond, 2005).

Persons with recurrent affective disorders are exposed to a very large stress load throughout their lives. The affective symptoms are the most characteristic and persistent stressors of these disorders and patients have been shown to suffer from affective symptoms about 50% of the time (Judd et al., 1998, 2003, 2002). Traditionally, research on affective episodes has focused on HPA-axis hyperactivity which also consistently has been reported (Daban et al., 2005; Pariante and Lightman, 2008); however, recent studies in other stress-related disorders have found that long-term chronic stress with frequent and persisting HPA-axis over activity can evolve into a state of generally low HPA-axis activity (Fries et al., 2005; Heim et al., 2000; Miller et al., 2007). This state, which has been referred to as hypocortisolism, has recently also been found to be common among affective patients in middle to old age (Maripuu et al., 2014; Oldehinkel et al., 2001; Penninx et al., 2007; Wikgren et al., 2012).

Long-term chronic stress exposure could be one of many etiological factors for both metabolic disorders and hypocortisolism. Before hypocortisolism has developed, HPA axis activity and cortisol levels can be expected to fluctuate between normal and high, depending on the current state of the stress exposure. Obesity and metabolic changes are much less prone to short-term fluctuations and can be expected to develop progressively with the accumulation of stress and cortisol exposure. Therefore, transient shifts in stress exposure and cortisol levels can be a confounder when addressing an association between stress, HPA-axis hyperactivity, and metabolic disorders. This could explain, despite significant research efforts, why there is no clear consensus concerning the possibility that obesity could be related to abnormal HPA-axis regulation (Abraham et al., 2013; Bjorntorp and Rosmond, 2000; Incollingo Rodriguez et al., 2015). However, hypocortisolism offers a possibility to identify individuals who have suffered from increased stress exposure and cortisol excess for extended periods and could therefore be expected to exhibit a higher frequency of obesity and metabolic abnormalities.

The mechanistic underpinnings of hypocortisolism are largely unknown, but two of the core characteristics have been found to be low basal cortisol levels and increased negative feedback sensitivity of the HPA-axis (Heim et al., 2000). A low dose dexamethasone suppression test (DST) has been proposed as the most sensitive measure of hypocortisolism (Fries et al., 2005). Interestingly, several studies that have used a low dose DST to study the general population have also found a relationship between low post-DST cortisol and high BMI or high WHR (Ljung et al., 1996; Pasquali et al., 2002; Rask et al., 2001).

As a first step in exploring the role of chronic stress and cortisol regulation for CVD in recurrent affective disorders, we focused on the relationship between hypocortisolism and metabolic cardiovascular risk factors. We hypothesized that relative hypocortisolism, as a sign of an elevated long-term accumulated stress exposure, would be associated with obesity, metabolic abnormalities, and the full metabolic syndrome in patients with recurrent affective disorders (n=245). The same hypothesis was also addressed in a control sample representative of the general population (n=258).

Table 1
Study participant characteristics.

	Patients (n=245)	Controls (n=258)	p
Age (SD)	53 (15)	53 (12)	0.466
Gender, male/female (% male)	98 (40)	132 (51)	0.012
Post-DST cortisol, nmol/l (*SD*)	338 (189)	311 (132)	0.064
Basal cortisol, nmol/l (*SD*)[a]	455 (162)	400 (110)	0.001
Smoking, *n* (%)	48 (20)	37 (14)	0.124
Number of subjects belonging to the hypocortisolism group (low post-DST group[b]), *n* (%)	70 (29)	66 (26)	0.483
Mean post-DST cortisol of the hypocortisolism group, nmol/L (*SD*)	127 (66)	156 (51)	0.005
Number of subjects belonging to the hypercortisolism group (high post-DST group[c]), *n* (%)	78 (32)	54 (21)	0.006
Mean post-DST cortisol of the hypercortisolism group, nmol/L (*SD*)	556 (125)	505 (78)	0.004
Number of subjects belonging to the non-hypocortisolism group (high and mid post-DST groups[d]), *n* (%)	175 (71)	192 (74)	0.483
Mean post-DST cortisol of the non-hypocortisolism group, nmol/L (*SD*)	422 (152)	364 (107)	< 0.001
Hypertension medication *n* (%)	48 (20)	44 (17)	0.490
Dyslipidaemia medication *n* (%)	17 (7)	20 (8)	0.737
Diabetes medication *n* (%)	10 (4)	5 (2)	0.194
Patient specific characteristics			
Recurrent depression diagnosis, *n* (%)	87 (35)	Na	Na
Bipolar disorder type 1 diagnosis, *n* (%)	97 (40)	Na	Na
Bipolar disorder type 2 diagnosis, *n* (%)	61 (25)	Na	Na
Disease duration, years (SD)[e]	26 (14)	Na	Na
Lithium medication, *n* (%)	118 (48)	Na	Na
Antiepileptic medication, *n* (%)	38 (16)	Na	Na
First generation antipsychotic medication, *n* (%)	18 (7)	Na	Na
Second generation antipsychotic medication, *n* (%)	24 (10)	Na	Na
SSRI medication, *n* (%)	50 (20)	Na	Na
SNRI medication, *n* (%)	22 (9)	Na	Na
Tricyclic anti-depressant medication, *n* (%)	18 (7)	Na	Na
Other anti-depressive medication *n* (%)	20 (8)	Na	Na

DST, dexamethasone suppression test; *SD*, standard deviation; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor. All values are means unless otherwise specified. Student's *t*-test was used when testing for differences between two means and Pearson's chi-square test was used when testing for differences in distribution of categorical data.

[a] Basal cortisol only evaluated in a subsample of patients; n=164 and controls n=136.

[b] Hypocortisolism defined as post DST cortisol below 221.75 nmol/l.

[c] Hypercortisolism defined as post DST cortisol above 408.75 nmol/l.

[d] Non-hypocortisolism defined as post DST cortisol above 221.75 nmol/l.

[e] Disease duration defined as time from first affective episode until date of examination.

2. Materials and methods

2.1. Study participants

The patient sample consisted of 245 patients with recurrent affective disorders: 97 (40%) bipolar type 1; 61 (25%) bipolar type 2; and 87 (35%) recurrent unipolar depression. The patients were between 19 and 82 years old (mean age=53) and 40% were males. For further description, see Table 1. All patients were outpatients without mania and hypomania. They were not related and did not use oral corticosteroid medication. Other exclusion criteria that could be mentioned were schizoaffective disorder, neurologic disorders affecting the central nervous system including dementia and mental retardation as well as any feature that would comprise the ability to fulfill the study protocol e.g. severe auditory or visual handicaps or not having Swedish as a mother tongue.