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Salivary cortisol profiles in patients remitted from recurrent depression: One-year follow-up of a mindfulness-based cognitive therapy trial

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ABSTRACT

Few studies have examined changes of diurnal cortisol profiles prospectively, in relation to non-pharmacological interventions such as mindfulness-based cognitive therapy (MBCT). Fifty-six patients remitted from recurrent depression (≥3 episodes) were included in an 8-week randomized controlled trial comparing MBCT plus treatment as usual (TAU) with TAU for depression relapse prophylaxis. Saliva samples (0, 15, 30, 45, 60 min post-awakening, 3 PM, 8 PM) were collected on six occasions (pre- and post-intervention, 3-, 6-, 9-, 12-month follow-up). Cortisol awakening response (*CAR*), average day exposure (AUC_{day}) and *diurnal slope* were analyzed with mixed effects models (248 profiles, 1–6 per patient). MBCT ($n = 28$) and TAU groups ($n = 28$) did not significantly differ with respect to baseline variables. Intra-individual variability exceeded inter-individual variability for the *CAR* (62.2% vs. 32.5%), AUC_{day} (30.9% vs. 23.6%) and *diurnal slope* (51.0% vs. 34.2%). No time, group and time by group effect was observed for the *CAR* and *diurnal slope*. A significant time effect ($p = 0.003$) was detected for AUC_{day}, which was explained by seasonal variations ($p = 0.012$). Later wake-up was associated with lower *CAR* (−11.7% per 1-hour later awakening, $p < 0.001$) and lower AUC_{day} (−4.5%, $p = 0.014$). Longer depression history was associated with dampened *CAR* (−15.2% per 10-year longer illness, $p = 0.003$) and lower AUC_{day} (−8.8%, $p = 0.011$). Unchanged cortisol secretion patterns following participation in MBCT should be interpreted with regard to large unexplained variability, similar relapse rates in both groups and study limitations. Further research is needed to address the scar hypothesis of diminished HPA activity with a longer, chronic course of depression.

1. Introduction

Hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) in depression has been challenged in recent reviews that pointed at modest effects and large heterogeneity between studies (Knorr et al., 2010; Stetler and Miller, 2011). Debate has been ongoing about whether HPA dysfunction should be considered as a vulnerability factor for depression, as a correlate of depressive state or as a scar marker of the chronic course of the disorder. In recent years, focus has shifted from challenge conditions such as the dexamethasone/corticotropin releasing hormone test (DEX/CRH test) to less invasive basal saliva cortisol measurements, with special emphasis on the cortisol awakening response (*CAR*), i.e. a concentration peak observed within the first 15–45 min after awakening. On the one hand, increased CAR in unaffected subjects at familial risk for depression lent support to the hypothesis of cortisol hypersecretion as a possible endophenotype for depression (Mannie et al., 2007; Vreeburg et al., 2010). Furthermore, elevated *CAR* in adolescents was observed to prospectively predict onset of depression during follow-up (Adam et al., 2010). On the other hand, support for the state marker hypothesis arose from normalization of the HPA axis during antidepressant treatment, with larger effect associated with larger improvement of depression and anxiety severity (Lenze et al., 2011; McKay and Zakzanis, 2010). There is strong

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evidence that antidepressants modulate the glucocorticoid receptor (GR) through different mechanisms and that restoring GR function might play a role in their therapeutic action (Anacker et al., 2011). Studies on the relationship between cortisol profiles and characteristics of depression have been controversial. A large cohort study first showed no association between the *CAR* and depression severity, chronicity and symptom profile, but significantly higher *CAR* among patients with comorbid anxiety disorders (Vreeburg et al., 2009a). The same group later focused on a dimensional model of depression and anxiety and suggested that a non-linear relationship between *CAR* and symptom dimensions might explain earlier negative findings (Wardenaar et al., 2011). Finally, a history of stressful life experiences might lead to persistent changes in cortisol profiles, as observed for early life events (Gerritsen et al., 2010), low socioeconomic trajectories (Gustafsson et al., 2010), and job and general life stress (Chida and Steptoe, 2009). Such long-term effects might be relevant to persistent *CAR* elevation among patients in remission from depression (Aubry et al., 2010; Bhagwagar et al., 2003).

A recent meta-analysis pointed at the important overlap of morning salivary cortisol levels between depressed patients and controls, while a small but statistically significant difference was confirmed (Knorr et al., 2010). Several large epidemiological surveys focused on inter-individual variability and its determinants (Kumari et al., 2010; Lederbogen et al., 2010; Vreeburg et al., 2009b). Numerous variables have been documented to influence cortisol secretion, including sociodemographic variables (e.g. sex and age), lifestyle parameters (smoking, physical activity, sleep duration), health factors (cardiovascular disease) and sampling conditions (working day vs. weekend, season). Information about intra-individual variability is scarcer. According to a large survey with saliva samples collected on four consecutive days, up to 78% of the total *CAR* variation might be attributed to day-to-day variability (Almeida et al., 2009). A study in older adults reported that the *CAR* might be sensitive to short-term effects, with prior-day feelings of loneliness, sadness, threat and lack of control associated with higher *CAR* the next day (Adam et al., 2006). Thus, lack of adjustment for relevant between- and within-subject variability factors might have accounted for low signal-to-noise ratio and inconsistent results in some earlier studies.

Not surprisingly, cortisol has been evaluated as a marker for improvement with various types of non-pharmacological treatment, such as interventions aimed at reducing stress. A recent article reviewed accumulating evidence that cortisol levels tend to decrease after a Mindfulness-Based Stress Reduction program (MBSR) (Matousek et al., 2010). Salivary cortisol was also included among possible predictors of brief cognitive therapy effectiveness in preventing relapse in recurrent depression (Bockting et al., 2006).

The present investigation was part of a study designed to confirm the efficacy of Mindfulness-Based Cognitive Therapy (MBCT) (Segal et al., 2002) compared with Treatment As Usual (TAU) in reducing relapse risk in patients remitted from at least 3 episodes of depression. We previously reported that participation in the MBCT program was associated with delayed relapse but unchanged relapse rate over the 14-month observation period (Bondolfi et al., 2010). A second aim of the study was to examine possible changes of diurnal salivary cortisol profiles, which were measured on 6 occasions over the follow-up period. Objectives of the present report were 3-fold: quantify within- and between-patient variability of different indices related to cortisol profiles; test for a possible change over time that might be specific to participants in the MBCT program; and examine the role of variables previously documented or as yet undocumented as relevant variability factors.

2. Materials and methods

2.1. Patients

Participants in the MBCT trial were recruited through media announcements and mailings to psychiatrists and general practitioners in the French speaking part of Switzerland. Inclusion criteria have been described earlier (Bondolfi et al., 2010) and can be summarized as follows: history of recurrent major depressive disorder according to DSM-IV (American Psychiatric Association, 1994); at least three past depressive episodes; remission since at least 3 months, with a score $\leq$13 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979); history of treatment by a recognized antidepressant drug, but being off medication for at least 3 months. The following non-inclusion criteria were considered: history of schizophrenia or schizoaffective disorder; current substance abuse, eating disorder or obsessive compulsive disorder; organic mental disorder, pervasive developmental disorder, borderline personality disorder; dysthymia with onset before age 20; $>$4 sessions of cognitive behavioral therapy ever; current psychotherapy or counseling; current practice of meditation or yoga.

The study was designed as a replication of two previous MBCT trials, with identical inclusion criteria (Ma and Teasdale, 2004; Teasdale et al., 2000). The rationale for including patients with 3 or more episodes was based on previous findings that MBCT allowed reducing relapse risk specifically in the ones with $\geq$3 episodes.

The study flow chart has been provided in our earlier publication (Bondolfi et al., 2010). Briefly, of 142 patients who completed a selection interview with an experienced clinical psychologist, 71 eligible participants entered a 3-month run-in period. Phone contact was maintained on a monthly basis to ascertain that remission was stable, in the absence of antidepressant medication. After the run-in phase, an enrolment interview took place to check that inclusion criteria were still met. Eleven patients were excluded (7 had relapsed; 2 refused to participate; 2 could not be contacted) and 60 were randomized to MBCT plus TAU or TAU.

The study protocol received approval from the ethics committee of the Geneva University Hospitals and each participant provided written informed consent before being enrolled.

2.2. Study design and intervention

Detailed information about the MBCT program and study procedures has been provided in our earlier publication (Bondolfi et al., 2010). Briefly, MBCT consists of 8 weekly sessions of a group intervention that integrates components of the MBSR program with elements of Cognitive Behavioral Therapy (CBT) to prevent depressive relapse (Segal et al., 2002). Participants were randomly assigned to TAU (unrestricted access to any type of treatment or help) or MBCT plus TAU. All therapists had participated to a training program, had experience running MBCT groups and had ongoing personal mindfulness practice. Four MBCT booster-sessions were provided at 3-month intervals during the 1-year follow-up.

Based on the main efficacy hypothesis of MBCT allowing to reduce relapse risk, sample size was estimated at 28 subjects per group (Bondolfi et al., 2010). Post-hoc power analysis indicated that for 28 MBCT participants, power would be 77% to detect a *CAR* normalization toward values observed in controls (effect size 0.53 in log-scale, based on data in Aubry et al., 2010; paired Student *t*-test, two-tailed, significance level at 5%).

2.3. Instruments

Patients were assessed at baseline (T1), at the end of the MBCT program (T2, month 2) and at 3-month intervals during a 1-year