Cortisol as a marker for improvement in mindfulness-based stress reduction

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A B S T R A C T

While much attention has been devoted to examining the beneficial effects of Mindfulness-Based Stress Reduction programs on patients' ability to cope with various chronic medical conditions, most studies have relied on self-report measures of improvement. Given that these measures may not accurately reflect physiological conditions, there is a need for an objective marker of improvement in research evaluating the beneficial effects of stress management programs. Cortisol is the major stress hormone in the human organism and as such is a promising candidate measure in the study of the effects of Mindfulness-Based Stress Reduction programs. In conjunction with other biological measures, the use of cortisol levels as a physiological marker of stress may be useful to validate self-reported benefits attributed to this program. In the current manuscript, we review the available literature on the role of cortisol as a physiological marker for improvement with regards to mindfulness practice, and make recommendations for future study designs.

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1. Cortisol production in relation to stressors and the stress response

The term "homeostasis" was coined to capture an organism's capacity to maintain certain bodily functions (e.g., body temperature, oxygen) within a narrow range via coordinated physiological mechanisms, despite disturbances in its internal and/or external environment.[1] The process by which this regulation is achieved is complex and our understanding of it has evolved markedly over the last century. Initially, Selye posited that, when the integrity of an organism is threatened by exposure to a physical or psychological stessor (e.g., facing a predator, exposure to intense cold), irrespective of the nature of that agent, the system responds in a generalized, non-specific fashion. This response consists of physiological and hormonal signals (e.g., glucocorticoids) in an effort to re-establish homeostasis in the body and adapt to these new conditions. In Selye's view, if the stressful event was ongoing, a prolonged "period of resistance", or adaptation to the stressor, follows. Continued exposure to the stressor, however, was postulated to result in eventual disease, as the organism succumbs to exhaustion ("general adaptation syndrome").[2–4] In an extension of

this work, McEwen refined Sterling and Eyer's term "allostasis",[5] or adaptation, and has argued that it is not repeated exposure to a stressor per se that leads to exhaustion, but rather it is the consequences of the repeated exposure to the chemical mediators associated with the stressor that lead to this state.[6]

The primary chemical mediators of allostasis include hormones of the hypothalamic–pituitary–adrenal (HPA) axis (e.g., cortisol), catecholamines (e.g., dopamine, epinephrine and norepinephrine) and cytokines. While providing the necessary energy to cope with the increases in demand in the short-term, exposure to these chemical mediators results in wear and tear on the body.[7] For example, in response to an acute stressor, the hypothalamus secretes corticotropin-releasing hormone (CRH), which travels to the anterior pituitary gland and stimulates the secretion of adrenocorticotrophic hormone (ACTH). ACTH, in turn, is released into the blood stream and eventually reaches the adrenal cortex, where it stimulates the release of cortisol. This release of cortisol in response to an acute stressor is believed to be involved in promoting survival functions, such as increasing blood pressure and blood sugar levels and promoting analgesia, while concurrently conserving energy from non-vital functions by suppressing reproductive, immune and digestive functions.[8,9]

However, despite their protective effects during times of increased demand, chronic elevations of glucocorticoids can have damaging effects on the body over time,[10,11] particularly when acute responses to stress become chronic.[7,12,13] Coupled with genetic risk factors, early developmental influences, and long-term

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use of maladaptive health behaviors (e.g., excessive alcohol consumption, smoking, poor diet), high levels of chemical mediators can be harmful, ultimately leading to disease and other negative health consequences (e.g., hypertension, diabetes, cardiovascular disease, receptor desensitization, tissue damage[6,11]).

Fortunately, many of these harmful effects are reversible, at least to some extent.[11] McEwen points to various lifestyle changes that people can make to decrease the adverse effects of chronic stress, including eating well, exercising regularly, and incorporating strategies for alleviating uncontrolled stress into their daily lives.[10,11] Mindfulness-Based Stress Reduction (MBSR) is a program that teaches people how to deal more effectively with stressors.

2. The Mindfulness-Based Stress Reduction (MBSR) model

The MBSR program, developed by Kabat-Zinn and colleagues at the University of Massachusetts Stress Reduction Clinic three decades ago, was designed to teach patients how to cope effectively with various chronic medical conditions (e.g., irritable bowel syndrome, chronic pain, cancer). Mindfulness is defined as a refined, systematic, attention-based strategy that focuses on the promotion of present moment awareness, in which thoughts, feelings and/or sensations that arise in the attentional field are to be acknowledged and accepted non-judgmentally.[14,15] The goal of mindfulness meditation practice is to reduce suffering by developing equanimity in the mind and body, as well as insight into the mental and physical conditions that inhibit an individual's capacity to respond pro-actively and effectively to everyday events.

When enrolled in a MBSR program, individuals with various illnesses are treated in a group setting for eight consecutive weeks. Generally, they meet weekly for 2.5 h per class, along with a silent retreat day held during week six of the course. The program includes the provision of theoretical material related to stress management and the mind–body connection, the practice of meditation in a group setting, daily home practice, as well as group dialogue and inquiry concerning weekly home assignments. Practicing various forms of meditation is considered an integral part of the program during and in-between classes.

3. Benefits of practicing mindfulness

From the program's inception, patients enrolled in MBSR programs at the University of Massachusetts Stress Reduction Clinic completed pre- and post-intervention questionnaires to assess efficacy.[16–19] Patient outcomes have been favorable, with self-reported reductions in physical (i.e., pain and other medical symptoms) and psychological symptomatology (e.g., decreases in depression, anxiety, perceived stress) reported following participation in MBSR programs in various centers around the world.[20–23] Results of a meta-analysis support the notion that MBSR may be beneficial for individuals coping with a wide variety of clinical and non-clinical problems.[24]

While self-report measures assess subjective responses to a given experience, some contend that these measures may not reflect bodily states in a valid or reliable manner.[25,26] Indeed, evidence indicates that there are often discrepancies between physiological measures and psychological perceptions of the same affective state, such as stress.[27–36] These discrepancies have been attributed to a number of different factors, including individual differences in perception and interpretation of visceral sensations,[33,37] social desirability,[38] dispositional anxiety,[39] personality,[40,41] the state of the individual,[36] and defensive style (i.e., repressors versus sensitizers[31]). Other researchers have raised questions regarding the validity of using self-report measures that necessitate retrospective evaluations of stress[42] and regarding the

test–retest reliability of the Perceived Stress Scale.[30] Thus, while resolving the discrepancies between objective physiological measures and subjective psychological perceptions of stress is a considerable challenge, observations regarding the relationship between them may afford investigators a better understanding of how stress management programs impact human physiological functioning. Since measurement of the activity of the HPA axis affords a more objective measure of the psychological state of the individual,[43] in this context, cortisol appears to be a promising outcome measure in the study of the effects of treatments intended to reduce stress, such as MBSR programs, as this hormone is secreted by the HPA axis in response to stress and has been found to be responsive to interventions geared towards reducing stress.[44]

4. Can salivary cortisol be an objective marker for stress reduction?

Various physiological responses have been studied in relation to the practice of MBSR including cardiovascular, brain, immune, and endocrine functions.[20,21,23,45–48] Given that cortisol is a hormone secreted in response to stress, we have chosen to evaluate the potential role of this hormonal mediator of the stress response as an objective marker for improvement in those who participate in a MBSR program by reviewing the extant literature on the subject. We acknowledge that cortisol is one of many interconnected hormonal mediators of the stress response (e.g., catecholamines, cytokines), but have selected it because it is relatively accessible to clinical researchers, and is an accepted objective biological marker of stress.

Likewise, we do not expect that the cortisol response would be unique to participation in a MBSR program, but rather would be evident following participation in other types of stress reduction interventions, as is evidenced by decreased cortisol levels following transcendental meditation and other Buddhist meditation practices,[49–53] yoga,[54,55] tai chi,[56] progressive relaxation training,[57] cognitive-behavior therapy,[54] and qi-training.[58,59] However, not all studies have found decreases in cortisol levels following these practices.[60,61] The fact that other stress reduction activities (e.g., yoga practice) can elicit similar positive psychological effects, without concomitant physiological effects (i.e., dance increased cortisol levels, whereas yoga decreased them), suggests that the amount of physiological arousal may be pertinent.[55]

4.1. Cortisol measurement

Cortisol has a strong circadian rhythm, with cortisol levels peaking during the first hour after awakening,[62] and decreasing for the rest of the day, with cortisol reaching its nadir around midnight.[8,63] Thus, careful consideration of time of testing is crucial as single assessments of cortisol levels are dependent on the time of day. To avoid these potential confounds, collecting saliva samples at multiple test times throughout the day to reflect differing points of the circadian pattern of cortisol secretion for 3–4 days is recommended.[64] Alternatively, repeated measurement of free cortisol levels within the 60 min after awakening in the morning is considered a stable and reliable biological marker of adrenocortical activity.[62]

Cortisol can be measured in urine, plasma, and/or saliva. In plasma, the majority of circulating cortisol is tightly bound to corticosteroid-binding globulin (CBG) and a smaller proportion is loosely bound to albumin. The remaining fraction ($<5\%$) is free, or unbound, and is thought to be available to exert biological activity.[65] Although absolute levels of cortisol found in saliva are significantly lower than those found in plasma, saliva cortisol is more closely correlated with the free fraction in serum than to total

serum cortisol.[66] Thus, salivary measures of cortisol are considered a valid and reliable alternative to measuring free cortisol in serum.[62,67–71]

Salivary cortisol sampling has distinct advantages over serum sampling, including its non-invasive nature and its lack of dependence on the availability of a healthcare professional.[66] Nonetheless, saliva samples can be affected by numerous factors, such as food intake, smoking, caffeine consumption, rigorous exercise, and timing of collection, such that protocol compliance is crucial to obtaining valid data. Thus, Hanrahan et al. suggest several strategies for increasing the validity of results derived from saliva sampling, including, but not limited to: standardizing the time for sample collection; using consistent collection materials and methods; and controlling for the confounding effects of certain drinks, foods, medications and diagnoses.[72] Additionally, electronic tagging of saliva sampling devices and use of actigraphy (i.e., motion sensors that detect the increase in physical activity associated with waking up to monitor the delay between waking and taking the waking sample) have been suggested to improve patient compliance and sampling accuracy,[73–75] as delays of more than 15 min between waking and sampling lead to attenuations in the cortisol awakening response.[76] However, Jacobs et al. demonstrated a relatively high level of concordance between electronically timed samples and self-reported compliance of saliva sampling times,[77] suggesting that these methods, despite being preferable, may be unnecessary.

5. Summary and critique of existing research on cortisol and MBSR

Table 1 summarizes the literature evaluating the effects of participation in a MBSR program on cortisol levels, systematically identifying variations in the sample, in the intervention, and in the methodology of cortisol assessment, along with the main research findings. There is accumulating evidence indicating that cortisol levels decrease following participation in a MBSR program. Carlson et al. related the effects of participation in a MBSR program on mood, quality of life, stress symptoms, cortisol levels, melatonin levels and dehydroepiandrosterone sulphate levels in 59 early stage breast cancer and 10 prostate cancer patients free of a concurrent mood or anxiety disorder.[45] Cortisol levels were measured pre- and post-intervention via salivary samples collected across one day at 8 am, 2 pm, and 8 pm. Although approximately 40% of the sample demonstrated abnormal elevations in diurnal cortisol secretion patterns both pre- and post-participation in the MBSR program, extreme cortisol levels were attenuated, with afternoon elevations of cortisol becoming less prevalent after completing the program. When these same patients were re-evaluated 6 and 12 months later, cortisol levels decreased systematically over the course of follow-up.[20] Similarly, 44 women recently diagnosed with breast cancer who participated in a non-randomized MBSR program had reduced late afternoon plasma cortisol levels compared to a control group receiving usual care.[23] Together, these findings suggest that participation in an MBSR program may have beneficial effects on the stress response and on the HPA axis, however the single day of salivary cortisol collection warrants replication using more rigorous cortisol sampling techniques involving multiple days of testing at each assessment period.[78]

Similar results were demonstrated when awakening salivary cortisol was used as a measure of adrenocortical activity. Marcus et al. evaluated the impact of a MBSR program on 21 participants receiving treatment for substance abuse in a residential therapeutic community and found that awakening salivary cortisol levels were significantly lower following the intervention.[30] While changes in perceived stress were evident albeit non-significant, these results

are of clinical importance because they provide further evidence that participation in a MBSR program may have beneficial impacts on participants' physiological responses to stress.

Not all researchers have reported beneficial effects of participation in a MBSR program on the HPA axis. For example, Galantino et al. found no significant changes in salivary cortisol levels from pre- to post-intervention in 42 healthcare professionals who completed the program.[79] Similarly, several investigators have failed to find group differences in basal cortisol levels between controls and participants following an 8-week MBSR program.[21,48] However, all three of these studies employed a single measure of salivary cortisol, which may have precluded their ability to detect changes in salivary cortisol levels. The use of a single measure of salivary cortisol is no longer deemed appropriate given the known diurnal rhythmicity and day-to-day variability in cortisol production.[66] The collection of repeated measurements per day over multiple days of testing pre- and post-participation in a MBSR program is suggested instead to obtain a more accurate reflection of cortisol regulation. Moreover, attention must be paid to the various potential confounding variables unrelated to the intervention of interest (e.g., diet, physical exercise, sleep–wake cycle) as these variables can independently affect salivary cortisol levels. Indeed, lack of control over confounding variables, such as diet and physical activity prior to cortisol sampling, may explain why Klatt et al. failed to find group differences in basal cortisol levels between 22 subjects who participated in a MBSR program and 20 controls following a 6-week program, despite their use of repeated saliva cortisol measures pre- and post-program.[80] Minimization of the risk of confounding variables is crucial to ensure valid cortisol data. Finally, other plausible explanations for the lack of findings regarding cortisol levels may include use of an abbreviated MBSR program [i.e., not the standard 8 weeks[80]] and small sample sizes, with 22 subjects who participated in a MBSR program and 20 controls in Klatt et al.[80] and 9 women per group in Robert-McComb et al.[48] Larger sample sizes, standard intervention times, and more intensive cortisol sampling techniques would bolster future studies for effects of MBSR.

While there are currently no studies examining MBSR-related changes in cortisol responsivity to acute stressors, experiments have demonstrated reductions in cortisol levels[49–51] and in systolic blood pressure, heart rate, and CO_2 reactivity[81] to acute psychological stressors in subjects who were either long-term regular practitioners of transcendental meditation or who were randomly assigned to practice transcendental meditation for the first time compared to controls. These physiological profiles are more in line with healthier neuroendocrine and cardiovascular profiles[82] and suggest that participation in a MBSR program might have similarly beneficial effects on cortisol responsivity to an acute stressor. Future studies are necessary to confirm this hypothesis.

5.1. Other markers of the stress response

Some researchers suggest that other markers, such as secretory immunoglobulin A (s-IgA),[83] or salivary amylase[84] may be better markers of stress and/or of the relaxation response than cortisol. Alpha-amylase is an enzyme found in human saliva that is secreted in response to stimulation of the sympathetic nervous system, and has been found to increase in response to a psychological stressor.[84–86] Indeed, Takai et al. found that salivary amylase levels were more significantly increased and reacted more rapidly than cortisol to an acute psychological stressor,[84] leading them to conclude that salivary amylase might be a better index of stress than cortisol. Relatedly, s-IgA, an antibody found in various secretory fluids such as saliva, has been found to respond to psychological stress. While there is discrepancy in the literature regarding

Table 1
Summary of studies investigating the effects of participation in a MBSR program on cortisol levels.

Article information	Sample	MBSR intervention	Cortisol assessments	Main findings re: cortisol	Main limitation(s)
Carlson et al.[45]	Fifty-eight and 42 patients were assessed pre- and post-intervention, respectively (baseline age: mean 54.5 years, SD 10.9 years)	An eight-week MBSR program that incorporated relaxation, meditation, gentle yoga and daily home practice.	Salivary cortisol was collected three times per day (8:00 am, 2:00 pm and 8:00 pm) for 1 day at each assessment period (at pre- and post-MBSR intervention).	Approximately 40% of the sample demonstrated abnormal cortisol secretion patterns both pre- and post-intervention, but within that group patterns shifted from "inverted-V-shaped" patterns towards more "V-shaped" patterns of secretion.	- The single day of salivary cortisol collection warrants replication using more rigorous cortisol sampling techniques involving multiple days of testing at each assessment period.
Carlson et al.[20]	Fifty-nine, 51, 47 and 41 patients provided data at pre- and post-intervention and at 6- and 12-month follow-up, respectively. (baseline age: mean 54.5 years, SD 10.9 years). Thirty-three patients provided data at all four time points for the endocrine measures.	An eight-week MBSR program that incorporated relaxation, meditation, gentle yoga and daily home practice.	Salivary cortisol was collected three times per day (8:00 am, 2:00 pm and 8:00 pm) at each assessment period (at pre- and post-MBSR intervention and at 6- and 12-month follow-up).	Cortisol levels decreased systematically over the course of the follow-up. MBSR program participation was associated with altered cortisol patterns consistent with less stress and mood disturbance.	- Single day of salivary cortisol collection (see above).
Witek-Janusek et al.[23]	Women diagnosed with early stage breast cancer participated in either the MBSR group ($n = 38$; age 55 ± 10 years) or the control group ($n = 28$; age 54 ± 8 years). Also, 30 age-matched healthy women who did not have cancer or a history of cancer (age 55 ± 9 years) participated in a cancer-free comparison group.	Women self-selected to participate in either 8-weekly (2.5 h/week) group MBSR sessions that incorporated the use of breath awareness, sitting and walking meditation, and mindful yoga (MBSR group), or into an assessment only control group (non-MBSR group).	Plasma cortisol (PM values) was measured only in those women whose blood was obtained in the late afternoon and/or evening (4–6 pm). This was done at four time points (pre-MBSR, mid-MBSR, post-MBSr and at 1-month follow-up).	Women enrolled in the MBSR program had reduced cortisol levels compared to the non-MBSR group. In comparison to the Cancer Free women, women in both the MBSR and the Non-MBSR groups had significant elevations of cortisol ($p < 0.05$) at all times.	- The use of a single measure of cortisol at a single time point is no longer considered as an acceptable method given the known diurnal rhythmicity and day-to-day variability in cortisol production - Lack of random assignment
Marcus et al.[30]	Twenty-one participants in a residential therapeutic community (mean age: 33 years).	An eight-week MBSR program that incorporated guided meditation focusing on bodily sensations/breath, sitting meditation, mindful Hatha yoga, walking meditation, and eating meditation.	Measured salivary cortisol at 0, 30, 45, and 60 min after awakening both pre- and post-intervention.	Awakening salivary cortisol levels were significantly lower ($P < 0.0001$) following the intervention.	- Small sample size
Galantino et al.[75]	Eighty-four employees from an institute within a university hospital	Eight weekly 2-h classes of a cognitive-behavioral stress management program based on MBSR principles.	Salivary cortisol was collected at one time point both pre- and post-intervention between 5 and 7 pm during sessions allotted for meditation practice.	A paired t-test between groups for pre/post-salivary cortisol yielded no significant change.	- The use of a single measure of cortisol at a single time point
Robert-McComb et al.[48]	Eighteen women (60 ± 6.3 years old) with documented histories of heart disease were randomly assigned to either a treatment group ($n = 9$) or a control group ($n = 9$).	The 8-week MBSR intervention included didactic, inductive, and experiential modes of learning regarding stress responses and mindfulness skill-development training.	Plasma cortisol was measured using a single morning blood sample.	There were no significant differences between groups in cortisol levels. However, there was a trend for change in the intervention group in the resting levels of cortisol that was not seen in the control group.	- The use of a single measure of cortisol at a single time point - Small sample sizes
Robinson et al.[21]	Individuals infected with the human immunodeficiency virus (HIV) either completed the MBSR intervention ($n = 24$; age 43 ± 6 years) or participated in the control group ($n = 10$; age 36 ± 8 years).	Participants self-selected to participate in either 8-weekly (2.5 h/week) group MBSR sessions that incorporated the use of body awareness, meditation, and yoga to teach mindfulness (MBSR group), or into a control group (non-MBSR group).	Plasma cortisol was measured using a simple blood sample collected within a specified time frame (1:00 pm to 5 pm).	No significant changes or differences were found for psychological, endocrine, or functional health variables.	- The use of a single measure of cortisol at a single time point - Lack of random assignment - Small sample sizes - 48% attrition rate

Table 1 (*continued*)

Article information	Sample	MBSR intervention	Cortisol assessments	Main findings re: cortisol	Main limitation(s)
Klatt et al.[80]	Working adults participated in either the MBSR-ld intervention (*n* = 22; age 43 ± 2 years) or a wait-list control group (*n* = 23; age 47 ± 2 years).	The intervention consisted of randomization to either a 6-week MBSR-ld program for 60 min, once per week that incorporated breathing, relaxation, body scans, and gentle yoga movement as facilitation toward a meditative state, or to a wait-list control group.	Baseline levels of salivary cortisol were established from 2 consecutive days of sampling conducted 20 min after awakening (approximately 7:00 am), at 1:00 pm, and at 10:00 pm. Salivary cortisol was sampled again at these same times once per week on the same day of the week during each week of the intervention, and again for 2 days at 1 week after completion of the intervention.	There were no changes in average daily salivary cortisol levels over time for participants in both groups and no differences from the pretest to the posttest.	- Abbreviated MBSR program - Small sample sizes - Confounding variables (e.g., diet, physical activity) not controlled for.

the utility of salivary s-IgA as a stress marker, with some showing salivary s-IgA increasing significantly after an acute psychological stressor,[85,87] and others showing either no change[88] or decreases,[89,90] some have argued that this discrepancy is due to methodological differences and that salivary s-IgA is a more suitable immunological marker for the immediate impact of stress than for its delayed effects.[83] Likewise, it has been argued that salivary s-IgA responds consistently to relaxation techniques and that it should be considered as a marker of the relaxation response.[83] If this is true, then salivary s-IgA might be an excellent candidate marker for evaluating the beneficial effects derived from stress reduction programs, such as the MBSR program, in addition to cortisol.

6. Conclusions

Herein we examined the potential role of cortisol as an objective marker for improvement in those who complete a MBSR program. When collected using rigorous methods, cortisol is a promising candidate to assess the effectiveness of interventions intended to reduce stress, such as MBSR, as this hormone is secreted by the adrenal glands in response to stress, has been found to be a reliable biological marker of adrenocortical activity, and has generally been found to be responsive to interventions geared towards reducing stress.[44] However, cortisol does not function in isolation, being one of several interconnected chemical mediators of the stress response that may be responsive to stress reduction interventions. Indeed, salivary immunoglobulin A, salivary amylase, dehydroepiandrosterone (DHEA), catecholamines, cytokines, and the other glucocorticoids are a few of the physiological mediators that work in concert with cortisol, and whose measurement may contribute to a more comprehensive understanding of the body's response to stress and to interventions designed to reduce stress, when coupled with self-report data.

Conflict of interest

None.

Role of the funding source

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