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Abstract

Objective: Chronic stress is widespread, and is detrimental to immune functioning and to overall physical and emotional health. These effects may be potentiated in patients with chronic illness, as high levels of chronic stress are common in this population. Numerous studies support the efficacy of mindfulness-based stress reduction (MBSR) in improving psychological functioning. If a strong relationship is found between MBSR and immune function, then MBSR may be implemented as a strategy to improve immune functioning and overall well-being. **Methods:** In the present review paper, the relationship between MBSR and immune function is evaluated. Empirical studies measuring immune markers as they relate to a standard MBSR intervention were reviewed. Relevant articles primarily involved patients with cancer or HIV. Therefore, the associations of immune measures with psychological distress are discussed, with an emphasis on patients with these conditions. A psychoneuroimmunological (PNI) framework was utilized to propose a mechanism for the relationship between MBSR and immune function. **Results:** Overall, the findings support a positive relationship between MBSR intervention and beneficial immunological outcomes. Variability in immune measures assessed across studies precludes pooling data to develop more conclusive results. **Conclusions:** MBSR has been shown to consistently improve emotional functioning and quality of life, and these effects appear to facilitate immune function.

Keywords: mindfulness, mindfulness-based stress reduction (MBSR), immune function, natural killer cells, mindfulness and cancer, mindfulness and HIV

1. Introduction

This literature review presents an investigation of the relationship between MBSR and immune function. This is the first literature review devoted to this important relationship. This is a salient area for study as it appears that MBSR affects psychosocial variables that correlate with immune functioning, and these relationships may represent critical aspects of fighting disease (Shannon, 2005; Sompayrac, 2003). Prior studies have established a strong link between psychological distress and reduced immune functioning (Gouin & Kiecolt-Glaser, 2011; Kiecolt-Glaser, Dura, Speicher, & Trask, 1991). This is particularly relevant in the case of chronic illness, such as HIV and cancer. These conditions are associated with immune supression (Robinson, Mathews, & Witek-Janusek, 2003; Sibinga et al., 2008; Witek-Janusek et al., 2008), and this may be compounded by emotional distress, which often accompanies these chronic illnesses (Boyer & Paharia, 2008). MBSR has no known risks (Praissman, 2008), and it has been shown to improve mood, stress levels, and quality of life (Carlson, Speca, Faris, & Patel, 2007; Reibel, Greeson, Brainard, & Rosenzweig, 2001). If evidence further supports a strong connection between MBSR and improved immune functioning, this may increase incentives for implementing MBSR programs in healthcare settings. The present paper is an evaluation of the existing evidence regarding the association between MBSR and immune functioning. Suggestions for future endeavors to enhance the evidence-base are provided.

2. Background

2.1 Mindfulness-Based Stress Reduction

MBSR stems from a structured 8-week program developed by Jon Kabat-Zinn at the University of Massachusetts Medical Center in 1979 (Kabat-Zinn, 1990). This program teaches individuals how to cope more effectively with stressors and fosters awareness of the present moment. It involves mindful meditation, relaxation, and hatha yoga (Kabat-Zinn, 1990; Matousek, Dobkin, & Pruessner, 2010). This program has been effective in treating healthy individuals with psychological distress, as well as medical patients with chronic pain, cancer, fibromyalgia, rheumatoid arthritis, heart disease, psoriasis, epilepsy, hypertension, and other chronic illnesses (Grossman, Nieman, Schmidt, & Walach, 2004; Matchim, & Armer, 2007; Praissman, 2008; Shennan, Payne, & Fenlon, 2010).

2.2 Relationship of Chronic Illness and Emotional Stress with Immune Function

Chronic illness may be emotionally challenging, and research supports the link between chronic psychological stress and immune suppression (Cohen, 2005; Glaser et al., 1987; Gouin, & Kiecolt-Glaser, 2011; Kiecolt-Glaser, 1991; Kiecolt-Glaser et al., 1987; Marucha, Kiecolt-Glaser, & Favagehi, 1998). Approximately 20-25% of cancer patients develop depressed mood or anxiety disorders (Antoni, 2003; Armaiz-Pena, Lutgendorf, Cole, & Sood, 2009; Colle et al., 2010; Shennan et al., 2010). Although there is no known connection between negative affect and cancer development, there is more clear evidence for psychological correlates with cancer progression once it has already been diagnosed (Carlson & Speca, 2011; Sephton, Sapolsky, Kraemer, & Spiegel, 2000). For instance, social support (Levy, Herberman, Whiteside, & Sanzo, 1990; Maunsell, Brisson, & Deschenes, 1995) and a fighting spirit are associated with longer survival rates, while suppression, helplessness, and hopelessness, are associated with an unfavorable progression (Carlson & Speca, 2011; Garssen, 2004; Greer, Morris, & Pettingale, 1979; Kieviet-Stijnen, Visser, Garssen, & Hudig, 2009; Ledesma & Kumano, 2009). Receiving an HIV diagnosis can also be a highly stressful event (Chida & Vedhara, 2009; Jam et al., 2010; Nott, Vedhara, & Spickett, 1995), and HIV/AIDS is frequently comorbid with psychiatric disorders. Approximately 22-45% of individuals with HIV/AIDS become depressed and 16 to 32% of this population experience anxiety (Boyer & Paharia, 2008). Recent literature supports an association between stress and HIV disease progression (Chida & Vedhara, 2009; Coates, Stall, Ekstrand, & Solomon, 1989; Irwin, Daniels, Smith, Bloom, & Weiner, 1987; Kemeny et al., 1994; Kemeny, Weiner, Duran, & Taylor, 1995). The link between psychological distress, immune functioning, and disease progression highlights the need to incorporate psychological interventions into treatment for chronic illness.

3. Review

3.1 Literature Search Methods

The present literature review was conducted using the following databases: PsycINFO, Science Direct, Wiley Online Library, PubMed, and Medline. Research in this area did not begin to flourish until the early 2000s. Therefore, peer-reviewed English language journal articles published between 2000 and 2011 were reviewed. Keywords in the search included mindfulness, meditation, MBSR, immune function, immune system, and natural killer cells. The following selection criteria were then applied: (a) peer-reviewed empirical study, (b) implemented a standard MBSR protocol based on Kabat-Zinn's (Kabat-Zinn, 1990) program, and (c) gathered pre- and post-intervention quantitative measures of immune function. Given these stipulations, the computerized database search yielded 8 studies. These articles primarily involved groups of heterogeneous patients, patients specifically with cancer or HIV, or healthy participants. Natural killer cell activity was the most commonly utilized immune marker, though there was much variation in other immune markers studied, and these selections were often based on the physical condition of the participant sample involved. To enhance clarity, the following section regarding the relationship between MBSR and immune function is divided into (a) NK cell comparisons among all relevant study samples, and (b) all other immune marker comparisons, categorized by health status of the sample.

3.2 MBSR and NK Cell Activity

Natural killer cells defend against specific intracellular infections, and they can also destroy lymphoid tumor cell lines (Buckingham, Gillies, & Cowell, 1997; Shannon, 2005). These cells have been the most frequently implemented immune marker for cancer progression because NK cells are cytotoxic to tumor tissue (Spiegel & Sephton, 2001) and because reductions in NK activity have been correlated with tumor progression, metastasis, and increased tumor burden (Anderson, Kiecolt-Glaser, & Glaser, 1994). Increases in NK cell activity and

number, on the other hand, often reflect an improvement in immune functioning (Alter et al., 2011; Fauci, Mavilio, & Kottilil, 2005; Robinson et al., 2003).

In a single-group pre- and post-MBSR intervention design with a heterogeneous patient sample (N = 24), the association between emotional status and immune function after completion of an 8-week MBSR program was evaluated (Fang et al., 2010). Psychological distress was measured with the Brief Symptom Inventory-18 (BSI-18; Derogatis, 2001) and quality of life was measured with the Medical Outcomes Survey Short-Form (SF-36; Ware & Sherbourne, 1992). Post-intervention results indicated significant reductions in anxiety (t = 3.40, p = 0.004) and overall distress, the latter of which was measured by the General Severity Index (t = 2.55, p = 0.023). There were also improvements in reported quality of life, as indicated by significant changes on the physical (t = -2.41, p = 0.029) and mental (t = -2.26, p = 0.039) composite scores. In terms of markers of immune function, there were no statistically significant overall changes in NK cells. However, improvements in the Mental Component Summary were correlated with significantly increased, and thus improved measures of NK cell activity, as measured by LU_{20} NK and LU_{20} PBMC (rs = 0.59 and 0.63, respectively, ps < 0.02). Improved measures of mental health were also significantly correlated with increases in LU_{20} NK and LU_{20} PBMC (rs = 0.69 and 0.71, respectively, ps < 0.01). This suggests that improvement in psychological well-being, upon completion of an MBSR program, was associated with increased and thus improved levels of NK cytolytic activity.

In a non-randomized controlled study evaluating the relationship between MBSR participation and immune function, 75 women with early stage breast cancer who had been treated with surgery (but who had not yet received chemotherapy), chose to either participate in an MBSR intervention group or in an assessment-only control group (Witek-Janusek et al., 2008). Thirty-eight women completed the MBSR intervention and associated measures, and 28 control participants completed relevant assessments. Participants also included 30 age-matched cancer-free individuals to serve as a non-intervention comparison for biological measures. Assessments included the Quality of Life Index Cancer Version III (Ferrans, 1990), Jalowiec Coping Scale (JCS; Jalowiec, Murphy, & Powers, 1984), and peripheral blood mononuclear NK cell activity (NKCA), and were conducted at four time points. MBSR participants reported better quality of life [F = 5.582; df (1, 45); p = 0.023], particularly in the psychological-spiritual [F = 12.493; df(1, 44); p = 0.001] and family [F = 4.214; df(1,44); p = 0.046] domains. There were also significant treatment effects for optimistic [F = 3.504; df(2, 94); p = 0.034] and supportive [F = 4.347; df(1, 50); p = 0.04] coping styles. In terms of NKCA measures, there was a significant main effect of treatment [F = 7.308; df(1, 47); p = 0.010] and a significant interaction effect between treatment and time [F = 3.480; df(3, 141); p = 0.018], indicating that by Time 4, the NKCA of women in the MBSR group was greater than that of women in the assessment-only group (p = 0.002). Importantly, at Times 3 and 4, the NKCA for the MBSR group, but not the assessment-only group, returned to levels that did not differ (p > 0.05) from the cancer-free comparison group.

Carlson and colleagues (Carlson, Speca, Patel, & Goodey, 2003) conducted a single group pre- and post-MBSR intervention design study, in which quality of life, mood, stress, and immune function were assessed in individuals with early stage breast (n = 49) and prostate (n = 10) cancer. Six- and 12-month follow-up assessments from this study were also reported in a 2007 paper (10). Assessment instruments included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; Aaronson et al., 1993), the Profile of Mood States (POMS; McNair, Lorr, & Droppelman, 1971), and the Symptoms of Stress Inventory (SOSI; Leckie & Thompson, 1979), and NK cell counts were measured. The results demonstrated significant post-MBSR improvements in overall global quality of life (t = -2.23, p < 0.05) and symptoms of stress (t = 3.23, p < 0.01), though no significant changes were evident in any of the POMS scores. The baseline POMS scores were already quite low, and the authors postulated that the lack of change may be related to a ceiling effect. In addition, there was no overall change in number of NK cells from pre- to post-intervention. The mean of the three post-MBSR quality of life scores were significantly improved, as compared to the pre-intervention EORTC score [F(1, 94) = 7.46, p < 0.005]. Significant improvements in overall stress also remained at one-year post-MBSR follow-up, and this was seen by the strong effect comparing the pre-intervention SOSI score to the average of the post-intervention scores [F(1, 85) = 16.30, p < 0.001). There was a significant quadratic effect across the post-intervention, 6-month, and 12-month follow-up periods for the NK cell levels, which initially increased and then decreased over time [F(1, 74) = 5.85, p < 0.05].

Robinson et al. (2003) used a non-randomized design in which patients with HIV selected to participate in either an MBSR intervention group (n = 24) or an assessment-only group (n = 10). All participants remained on the regular dosage of antiretroviral medication. Data were collected at pre-intervention and post-intervention, or at matched times for the assessment-only group, so that within-group and between-group measures could be

assessed. Outcome measures included the Perceived Stress Scale (PSS; Cohen & Williamson, 1988), POMS (McNair et al., 1971), and the Functional Assessment of HIV Infection (FAHI; Peterman, Cella, Mo, & McCain, 1997). Immune markers included NK cell activity and number. The immune markers were determined by standard chromium release assay and by flow cytometric phenotypic analysis with anti-CD56 and anti-CD16 antibodies, respectively. No significant within-group changes or between-group differences were found for psychological or functional health factors. The authors reported a trend toward an improvement in both POMS and FAHI scores, and indicated that the effects on PSS may have been weakened by virtue of termination and thus the end of a group support system. Statistical power was insufficient to determine changes in all the outcome variables because of the small sample size. However, NK cell activity and number improved both within-MBSR group (t = -2.64, p = 0.015 and t = -3.98, p = 0.001, respectively) and between groups (t = 2.05, p = 0.049 and t = 3.72, p = 0.001, respectively) when compared to the assessment-only group. In fact, while NK cell number and activity increased in the MBSR group, it decreased in the assessment-only comparison group. This result suggests that MBSR may be a viable adjunct strategy for improving immune function in individuals with HIV.

3.3 MBSR and Other Markers of Immune Function

3.3.1 Heterogeneous Patient Population

In the Fang et al. single-group pre- and post-MBSR intervention study (Fang et al., 2010), levels of C-reactive protein (CRP) were also examined in relation to changes in psychological distress and quality of life in a heterogeneous patient sample. CRP is the most commonly utilized acute-phase reactant marker of inflammation in the body. It mimics the action of antibodies, except it has a wider range of pathogen molecules to which it can attach. Increased circulating levels of CRP are indicative of an infection or systemic inflammatory response (Hapuarachi, Chalmers, Winefield, & Blake-Mortimer, 2003). This increase has been correlated with recurring coronary events post-myocardial infarction (Liuzz, Biasucci, & Gallimore, 1994) and increased risk of diabetes (Freeman, Norrie, & Caslake, 2002), but positive outcomes in patients with cancer (Scott et al., 2002). The Fang et al. results indicated that, although there was no statistically significant treatment-related change in CRP level for the sample as a whole, reductions in CRP correlated with reductions in anxiety and overall distress (rs = 0.64 and 0.52, respectively; $ps < 0.05$). Improvement in psychological well-being following an MBSR program was therefore associated with improved levels of CRP.

3.3.2 Cancer Patient Population

Studies have supported that MBSR has a positive impact in areas such as stress, anxiety, depression, and sleep for cancer patients and survivors (e.g., Branstrom, Kvillemo, & Moskowitz, 2010; Shennan et al., 2010). Studies have also found promising associations between MBSR and various markers of immune function in this patient population.

In addition to NKCA, Witek-Janusek and colleagues (Witek-Janusek et al., 2008) measured IFN-γ, IL-4, IL-6, and IL-10 immune markers in a non-randomized controlled design study. IFN-γ is a cytokine important for immunity against viral and intracellular bacterial infections, as well as for tumor control. With regard to interleukin functions, IL-4 stimulates the proliferation of B-cells and T-cells, as well as the differentiation of CD4 cells into Th2 cells, which in turn, produce additional IL-4 cells. IL-6 may act as both a pro-inflammatory and anti-inflammatory cytokine (Sompayrac, 2003). Secretion by T cells and macrophages in response to tissue damage leads to inflammation. As an anti-inflammatory cytokine, on the other hand, it is mediated through its activating effects on IL-1 and IL-10, as well as through its inhibiting effects on TNF-α and IL-1 (Shannon, 2005; Sompayrac, 2003). This interleukin is involved in diabetes, atherosclerosis, depression, lupus, and rheumatoid arthritis, as well as prostate and metastatic cancer (Shannon, 2005). IL-10 is an anti-inflammatory cytokine, which has the potential to inhibit pro-inflammatory cytokines, to reduce antigen markers, and to activate T cells, mast cells, and B cells (Shannon, 2005; Sompayrac, 2003). Participants included an MBSR early-stage cancer patient group (n = 38), an assessment-only early-stage cancer patient group (n = 28), and a cancer-free biological measure comparison group (n = 30). Study results showed that there was a significant increase in PBMC production of IFN-γ in the MBSR group, as compared to the assessment-only group, with both a significant main effect for treatment [F = 8.193; df(2, 59); p = 0.001], and an interaction effect between treatment and time [F = 2.981; df(6, 77); p = 0.043]. Furthermore, at the 4-week post-MBSR follow-up, the IFN-γ levels for the MBSR group, but not for the assessment-only group, were comparable to those of the cancer-free comparison group (p > 0.05). Results also indicated a significantly lower, and thus improved, level of interleukins produced by the PBMC cells in the MBSR group, as compared to the assessment-only group. There were main treatment effects for IL-4 [F = 12.420; df(1, 33); p = 0.001], IL-6 [F = 5.091; df(1, 33); p = 0.031], and IL-10 [F = 4.822; df(1,

33); $p = 0.035$]. Importantly, at the 4-week post-MBSR follow-up, each of these PBMC interleukin immune marker levels in the MBSR group, but not in the assessment-only group, were equivalent to those in the cancer-free comparison group ($p > 0.05$ for IL-4, 6, and 10; Witek-Janusek et al., 2008).

In the Carlson et al. (2003) single group pre- and post-MBSR intervention design study, measures of immune function (aside from NK count) included NKT, B, T total, T helper, and T cytotoxic cell counts, as well as NK and T cell production of TNF, IFN-γ, IL-4, and IL-10. The post-MBSR follow-up results (Carlson et al., 2007) revealed no significant change in the overall number of lymphocytes or cell subsets. However, there was a significant increase in T cell production of anti-inflammatory IL-4 ($t = -3.13$, $p < 0.01$), as well as a significant decrease in pro-inflammatory IFN-γ ($t = 2.18$, $p < 0.05$), and NK cell production of IL-10 ($t = 2.22$, $p < 0.05$). There was also a significant decrease in number of monocytes ($t = 2.26$, $p < 0.05$) and an increase in number of eosinophils ($t = -2.23$, $p < 0.05$), both trends which continued at one-year follow-up [$F(1, 79) = 6.74$, $p < 0.01$ and $F(1, 155) = 21.31$, $p < 0.001$, respectively]. These results support a change in cancer-related cytokine proliferation following MBSR participation. Unlike more recent studies, there were no significant correlations between psychological and immunological change scores at the $p < 0.01$ level.

3.3.3 HIV Patient Population

Several studies have also evaluated the relationship between MBSR and immune function in individuals with HIV. In a pilot study conducted in Iran, the CD4 immunological effects of an 8-week MBSR program were examined in a single group of patients ($n = 6$) who tested positive for HIV. Assessment times included pre- and post-intervention, as well as 3-, 6-, 9-, and 12-month follow-ups. At each assessment period, the CD4 level means were 549.0 ($SD = 173.6$), 640.2 ($SD = 189.4$; $p = 0.01$), 655.3 ($SD = 183.4$; $p = 0.001$), 638.0 ($SD = 167.4$; $p = 0.004$), 619.3 ($SD = 163.2$; $p = 0.004$), and 595.2 ($SD = 165.6$; $p = 0.04$), respectively. No patients received antiretroviral therapy, and the researchers inferred that changes in CD4 levels were associated with MBSR program participation (Jam et al., 2010).

These findings are consistent with a recent single-blind randomized control trial design to test the effects of an 8-week MBSR program ($n = 25$) compared to a 1-day control stress-reduction education seminar ($n = 15$) on CD4+ T lymphocyte counts in emotionally stressed individuals with HIV (Creswell, Myers, Cole, & Irwin, 2009). Assessments were conducted at matched time points before and after the MBSR intervention. At baseline, both groups endorsed moderate levels of distress ($M = 9.8$, $SD = 3.7$), measured with the Patient Health Questionnaire-9 (PHQ-9; Spitzer, Williams, Kroenke, & Hornyak, 2000). Results indicated that while CD4+ T lymphocytes declined in the control seminar group (ranging from $M_{pre\text{-}seminar} = 757$, $SE = 70$ to $M_{post\text{-}seminar} = 572$, $SE = 71$), levels remained stable in the MBSR group from pre- to post-intervention ($M = 618$, $SE = 47$ to $M = 628$, $SE = 52$ cells/mm^3, respectively). This shows a significant time X treatment interaction effect [$F(1, 45) = 5.70$, $p = 0.02$]. In addition, higher rates of attendance among the MBSR group were associated with greater CD4+ T lymphocyte levels [$t(74) = 2.09$, $p = 0.04$] post-intervention. This suggests that MBSR may be useful as an adjunct treatment to attenuate the decline of CD4+T lymphocyte cells in individuals with HIV.

Robinson et al. (2003) conducted a non-randomized study, in which patients with HIV elected to participate in either an MBSR intervention group ($n = 24$) or an assessment-only group ($n = 10$). In addition to NK cell number and activity, RANTES (regulated upon activation, normal T-cell expressed and presumably secreted) and Stromal-Derived Factor (SDF-1) immune markers were measured. The RANTES represents chemokines that compete with HIV for the chemokine receptor type 5 (CCR5) on lymphocytes, while SDF-1 facilitates the spread of HIV (Rowland-Jones, Pinheiro, & Kaul, 2001). Therefore, an increase in RANTES and a decrease in SDF-1 would indicate improved immunity. The results yielded a significant within-group post-MBSR increase in RANTES ($t = -2.66$, $p = 0.015$), while SDF-1 levels remained stable ($t = -0.44$, $p = 0.666$). However, there were not within-group changes for the assessment-only comparison group on the measures of RANTES or SDF-1. Due to the small sample, there were no significant between-group differences. This study provides limited evidence that MBSR may facilitate improvement in immunity among individuals with HIV.

3.3.4 Healthy Participants

Davidson et al. (2003) conducted a randomized controlled study examining the effects of an 8-week MBSR program (n=25) on immune function, compared with a wait-list control group ($n = 16$), in healthy employees at a biotechnology corporation. At the conclusion of the MBSR program, individuals in both groups were injected with the influenza vaccine and antibody titer response levels were obtained 4- and 8-weeks later. The MBSR group exhibited a significantly larger increase in antibody titers between weeks 4 and 8 following the vaccination, as compared to the controls [$t(33) = 2.05$, $p < 0.05$]. These findings support beneficial effects of MBSR on immune function.

4. Discussion

There is strong support for improved anxiety, stress, and quality of life following MBSR intervention (e.g., Carlson et al., 2003; Fang et al., 2010; Witek-Janusek, 2008). There is mixed support, however, in terms of beneficial immune changes post-MBSR intervention, suggesting a small overall effect (Carlson et al., 2003; Fang et al., 2010; Robinson et al., 2003; Witek-Janusek et al., 2008). Although each of the 8 studies reviewed showed some improvement in immune function, the specific changes were variable. Of the 5 studies that included measures of NK cell activity, two demonstrated significant improvement (Robinson et al., 2003; Witek-Janusek et al., 2008) and one showed significant improvement only when correlated with beneficial emotional changes (Fang et al., 2010). Carlson's 2003 study did not show significant changes in NK levels at post-MBSR intervention, though the 2007 follow-up paper (Carlson et al., 2007) displayed a significant quadratic effect. Also unlike the other studies, this one showed no significant correlation between psychological and immunological changes. However, in evaluating the current literature base as a whole, there was a trend toward favorable immune changes in those individuals who exhibit a greater improvement in psychological status. This is indicative of a more moderate effect of MBSR on improved immune function in individuals who also gain the most psychological benefit. Natural killer cell activity (Fang et al., 2010; Robinson et al., 2003; Witek-Janusek et al., 2008), as well as CRP (Fang et al., 2010), interferon (Witek-Janusek et al., 2008), interleukin (Witek-Janusek et al., 2008), RANTES (Robinson et al., 2003), and CD4 (Jam et al., 2010, Creswell et al., 2009) levels appear moderately correlated with improvements in anxiety and distress following a standard MBSR intervention.

4.1 Proposed Mechanisms

Stressful stimuli can adversely impact physiological functioning and overall health (Robinson et al., 2003, Webber, 2010) through chronic activation of the sympathetic nervous system and hormone-release in the hypothalamic-pituitary-adrenal (HPA) axis (Buckingham et al., 1997; Fang et al., 2010), as well as through maladaptive coping behaviors (Kendall-Tackett, 2010). On the other hand, these pathways may also account for the mechanism by which psychotherapy can positively influence health. Research indicates that MBSR prevents negative neuroendocrine-immune and behavioral effects related to chronic stress through relaxation and shifts in cognitive, emotional, biological, and behavioral domains (Witek-Janusek et al., 2008). This has been supported by numerous studies demonstrating the psychological benefits associated with MBSR practice. Both healthy and chronically ill MBSR participants have experienced significant reductions in stress, anxiety, and depression (Carlson et al., 2003; Carlson, Speca, Patel, & Goodey, 2004; Matousek et al., 2010; Speca, Carlson, Goodey, & Angen, 2000;, Tacon, Caldera, & Ronaghan, 2004). Practice in MBSR has also been associated with positive states of mind (Branstrom et al., 2010; Kieviet-Stijnen et al., 2008), emotional adjustment (Matousek et al., 2013; Tacon et al., 2004), a fighting spirit (Carlson et al., 2011), an internal locus of control (Carlson et al., 2004), and a better subjective quality of life (Carlson et al., 2004; Cohen et al., 2005). Such effects are correlated with improved psychosocial and health outcomes (Greer et al., 1979).

Given the well-established association between psychosocial factors and immune function, these beneficial psychosocial outcomes may explain the above findings of improved immune functioning in MBSR participants (e.g., Fang et al., 2010; Witek-JAnusek et al., 2008). Studies indicate that this process may be mediated by the neuroendocrine system, particularly through those components related to the stress response. High levels of cortisol, for instance, have been associated with stress, depression, and immune suppression, and such elevations have been found in 75% of a sample of metastatic breast and ovarian cancer patients (Touitou, Bogdan, Levi, Benavides, & Auzeby, 1996).

This mechanism is further supported by growing evidence that cortisol levels decrease following participation in an MBSR program (Matousek et al., 2010; Robinson et al., 2003). For instance, Carlson et al. (2007) found that in a single subject pre- and post-MBSR intervention with 6- and 12-month follow-ups in early stage breast or prostate cancer patients (N = 59), cortisol levels decreased consistently. There were significant decreases in average cortisol levels from baseline to post-MBSR [$F(1, 88) = 19.85$, $p < 0.001$] and at one-year follow-up [$F(1, 28) = 32.50$, $p < 0.001$].

4.2 Implications and Future Directions

Overall, the findings support a relationship between MBSR practice and beneficial immunological outcomes. This is important because optimal immune functioning will enhance disease-prevention and the fight against existing illness. Such an association is particularly relevant in today's high stress environment, which is often amplified by chronic illness (Boyer & Paharia, 2008). Individuals with chronic illnesses such as cancer or HIV may be at a greater risk for a spiral of increasing stress and immune dysregulation (Boyer & Paharia, 2008;

Robinson et al., 2003; Shannon et al., 2005). MBSR has no known adverse side-effects (Praissman, 2008), and it may therefore serve as an important complementary treatment to break this negative cycle and improve health outcomes.

Several limitations are present within the reviewed research studies, and this often involves the use of study designs and measures based on convenience. Despite the existence of only a limited number of studies in this area, there is much variability in the choice of outcome measures, which precludes pooling data to develop more conclusive results. This is especially troublesome due to the small sample sizes in the majority of studies, as well as much variability in the sample populations and study designs utilized. Some studies implemented single-group pre- and post-assessments, while others used an assessment-only control group. A major limitation in not including a control group is that it precludes the ability to infer causation related to any changes following participation in the MBSR program. In addition, nonspecific factors such as group interaction, expectancy effects, and therapeutic alliance, may have beneficial effects and cannot be controlled for in a single group design. However, even when a control group was used, the majority of the studies were non-randomized. The frequent participant self-selection between MBSR and assessment-only groups may have decreased validity related to sampling bias.

Given the consistent limitations of these studies, the need for statistically rigorous randomized controlled studies and larger sample sizes is important in order to more firmly determine the effects of MBSR on immune function. It may be helpful to examine the different components of MBSR to determine what the most effective aspects are in enhancing both physical and psychological outcomes. This strategy should also be compared to other treatment modalities to see whether other techniques might be just as effective.

Future studies (Table 1) may examine whether mediators, such as change in sleep quality, impact the significant correlations between psychological functioning and immune markers. This may lead to more targeted treatment interventions. Importantly, studies that involve longer-term follow-up may help to determine the extent to which relevant biological changes impact disease outcomes. It may also be interesting to track whether MBSR-related changes in immune markers, such as reduced inflammation, might be directly related to changes in specific disease outcomes.

Table 1. Ongoing randomized clinical trials of MBSR and immune function

Investigator(s)	Condition	Patients	Purpose	Study Completion Date
Fang C[67]	Cervical Dysplasia	300	To compare mindfulness-based stress with general health education in improving immune response to human papillomavirus in patients with cervical dysplasia.	August 2012
Moynihan JA[68]	Psoriasis	200	To examine and compare the effects of the MBSR program and the Living Well (LW) program on adults with psoriasis in terms of how these programs may affect their psoriasis, immune function, physical and emotional health, and well-being.	March 2013
Lengacher CA[69]	Breast Cancer	300	1) To determine the efficacy of the MBSR program in improving psychological and physical symptoms, quality of life and measures of immune function and a stress hormone (cortisol) 2) To determine whether positive effects achieved from the MBSR program are mediated through changes in mindfulness and fear of recurrence of breast cancer. 3) To determine whether positive effects achieved from the MBSR program are modified by specific patient characteristics measured at baseline	December 2013

Overall, this review indicates a positive relationship between MBSR and immune function (Creswell et al., 2009; Davidson et al., 2003; Jam et al., 2010; Robinson et al., 2003; Witek-Janusek, 2008). Though more rigorous studies are needed, there is evidence that the mechanisms by which MBSR is effective may include improvement in coping skills, mood, and stress levels (Carlson & Speca, 2011). This approach may enhance a patient's ability to take an active role in personal healthcare and maintain quality of life.

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