Abstract. Mindfulness-based stress reduction, a complementary and alternative therapy, is able to decrease cancer-related fatigue, and stress and to improve the quality of life in cancer patients. Some studies evaluated if mindfulness-based stress reduction could improve some cardiometabolic and cancer risk factors, including systemic chemokines, growth factors, and pro-inflammatory biomarkers (e.g., C-reactive protein, Interleukin-1). In this narrative review, we highlight the pleiotropic beneficial effects of mindfulness-based stress reduction and its clinical impact on cardiovascular and cancer risk factors among patients with cancer in different stages. Moreover, improvements in the overall quality of life, sleep quality, and immune functions [changes in plasma levels of interleukin-4 (IL-4), interferon-γ (INF-γ), and interleukin-10 (IL-10)] will also be discussed. Albeit few clinical studies available in the literature, evidenced the beneficial effects of mindfulness-based stress reduction on the immune and cardiometabolic profile in cancer patients, providing important insights into the closest collaboration between psycho-oncologists, oncologists, and cardiologists.

Key Words: Psychology, Cancer, Inflammation, Mindfulness, Risk factors.

Introduction

Despite improvements in anticancer pharmacological therapies, cancer remained the second cause of death in the United States in 2020, after cardiovascular diseases. Cancer patients experienced cancer-related and anticancer drug-related symptoms, ranging from pain, mucositis, cardiovascular diseases (i.e., heart failure, myocarditis), endocrine diseases, and others. Moreover, cancer patients are exposed to a high risk of depression and fatigue after cancer diagnosis and therapies. Recent data described that cancer patients have a four times higher risk of depression than the general population. Unfortunately, only 25% of patients receive a formal diagnosis of depression. Therefore, the epidemiological data actually available in the literature should be underestimated. Depression is associated with a high risk of mortality and a poor prognosis in patients with cancer. Therefore, clinical management of depression should be done in order to improve overall survival and quality of life (QoL) (Figure 1).

Mindfulness-based interventions (MBI) have emerged as promising interventions for cancer-related distress and affective disorders, and the literature is full of research supporting MBIs in improving depressive symptoms, fatigue, and life expectancy in patients with cancer. Some uncontrolled studies have also demonstrated positive alterations in physical health indicators, such as immune functions and cortisol levels, as a result of mindfulness training. However, the effect of MBI on hormone secretion and potentially beneficial changes in the hypothalamic-pituitary-adrenal cortex axis (HPA) is still largely unknown. Cortisol levels have been found to be linked to psychological well-being and seem, in particular, sensitive to negative emotional conditions. Dysregulation of the HPA axis and cortisol hormone levels have been reported in cancer patients, especially a flattening of the circadian rhythm of cortisol secretion and high systemic levels of cortisol. The clinical effects of HPA axis dysregulation in cancer patients are largely unknown; however, one study reported a significantly decreased survival among metastatic breast cancer patients with a flattened circadian rhythm of cortisol secretion. After analyzing the effects of...
BMI on cancer patients, it was found that it could be clinically beneficial after three and six months. Specifically, after three months of MBI therapy, patients saw a reduction in Post Traumatic Stress Disorder (PTSD) symptoms and an improvement in their quality of life (QoL). As a secondary outcome of the study, salivary cortisol was determined before and during MBI in these patients; authors described that salivary cortisol has been shown to be a convenient and reliable way to measure cortisol levels and a good marker of HPA axis homeostasis.

**Methods**

A systematic search of the Medline and EMBASE databases was performed to identify all potentially relevant English-language scientific papers containing original articles on the effect of Mindfulness on cancer and cardiovascular diseases. The following search strings were used in PubMed: “Mindfulness OR Meditation AND cancer” OR “Mindfulness OR Meditation AND cortisol” OR “Mindfulness OR Meditation AND cardiovascular”. The same research criteria were applied to Clinical Trial Register. The databases were last accessed on 28 February 2023.

**Biochemical Effects of Mindfulness-Based Interventions: an Overview**

Mindfulness-based interventions exert several beneficial effects on humans\(^1\). As summarized in Figure 1, mindfulness-based interventions reduce stress and systemic inflammation through many biochemical pathways. In summary, mindfulness-based interventions reduce the hypothalamic secretion of corticotropin-releasing hormone.

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**Figure 1.** Main biochemical pathways of mindfulness-based interventions. In brief, mindfulness-based interventions decrease CRH-ACTH-Cortisol axis that reduces NLRP3 inflammasome activation in the body; a reduction in NLRP3 levels decreases systemic levels of IL-6, IL-1, IL-8, and TNF-α. On the other hand, mindfulness-based interventions increase vagus nerve, which reduces sympathetic activity in the autonomous nerve system; vagus nerve activation reduces NF-κB/NLRP3 inflammasome signaling pathway, determining anti-inflammatory systemic effects.
(CRH), which in the pituitary gland inhibits adrenocorticotropic hormone (ACTH) synthesis and secretion\textsuperscript{21}. Once in the circulation, lower levels of ACTH reduce cortisol secretion in adrenal glands, resulting in stress reduction inhibition of the NLR family pyrin domain containing 3 (NLRP-3) inflammasome levels (a key player in inflammation and cardiovascular disease\textsuperscript{22}). Reduction of the NLRP3 inflammasome results in low levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 (IL-1) and tumor necrosis alpha (TNF-\(\alpha\))\textsuperscript{23}.

On the other hand, mindfulness-based interventions activate the vagus nerve\textsuperscript{24}. Activation of the vagus nerve reduces sympathetic tone and activates parasympathetic tone in the autonomic nervous system\textsuperscript{25}. Activation of the parasympathetic system results in suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)/NLRP3 inflammasome\textsuperscript{26} signaling pathway, which reduces systemic levels of IL-6, IL-8, INF-\(\gamma\), and TNF-\(\alpha\) resulting in decreased hepatic synthesis of ultrasensitive C-reactive protein (hs-CRP)\textsuperscript{27}.

### Cortisol Levels and Mindfulness-Based Interventions in Cancer Patients

Cancer patients experienced psychological stress at different levels before, during, and after cancer therapies, with significant changes in family relationships as well as in the daily management of life\textsuperscript{28}. MBI is a complex of psychological interventions aimed at reducing stress and improving QoL in patients with acute and chronic diseases\textsuperscript{29}. As summarized in Table I, recent meta-analyses\textsuperscript{30,31} concluded that MBI is effective in reducing stress, cortisol levels, and depression as well as in improving QoL. Some uncontrolled studies\textsuperscript{32,30} confirmed that MBI is able to reduce cortisol levels and improve immune functions in patients with and without cancer. Recent studies\textsuperscript{33,34} in patients with type 2 diabetes and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection demonstrated that mindfulness-based stress reduction (MBSR) intervention significantly improved anxiety, depression, and stress, and reduced systemic cortisol levels.

Another recent study of 70 adult patients with low back pain demonstrated that 12 months of MBSR reduced systemic cortisol and Interleukin 1\(\beta\) (IL-1\(\beta\)) levels than the untreated group\textsuperscript{35}. Moreover, MBSR reduced depression, stress, and perceived pain, improving general physical functions as well as sleep quality; the overall picture of this study indicates that MBSR could be an alternative and complementary medicine to improve pain and QoL in patients with low back pain\textsuperscript{35}. A study in woman veterans at high risk of cardiovascular diseases concluded that MBSR decreased diurnal salivary cortisol and interleukin-6, indicating strong anti-inflammatory and potential cardioprotective effects of MBSR\textsuperscript{36}. A randomized

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<thead>
<tr>
<th>Study (Ref)</th>
<th>Population</th>
<th>Clinical Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Grossman et al\textsuperscript{30}</td>
<td>Healthy population</td>
<td>Reduction of stress, cortisol levels and depression. Improvement of QoL</td>
</tr>
<tr>
<td>Ledesma and Kumano\textsuperscript{11}, Yuan et al\textsuperscript{32}</td>
<td>Patients with and without cancer</td>
<td>Reduction of cortisol levels, Improvement of immune functions</td>
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<tr>
<td>Suh et al\textsuperscript{33}, Sayadi et al\textsuperscript{34}</td>
<td>Type 2 diabetes and SARS-CoV-2 infection</td>
<td>Reduction of anxiety, depression, stress, and reduction of systemic cortisol levels</td>
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<tr>
<td>Díez et al\textsuperscript{35}</td>
<td>Healthy adult subjects</td>
<td>Reduction of systemic cortisol and Interleukin 1(\beta) (IL-1(\beta)) levels</td>
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<td>Saban et al\textsuperscript{36}</td>
<td>Woman veterans at high risk of cardiovascular diseases</td>
<td>Reduction of diurnal salivary cortisol and interleukin -6</td>
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<tr>
<td>Garland et al\textsuperscript{37}</td>
<td>Cancer survivors</td>
<td>Reduction of systemic cortisol levels</td>
</tr>
<tr>
<td>Lipschitz et al\textsuperscript{38}</td>
<td>Cancer survivors with sleep disturbance</td>
<td>Reduction in cortisol levels and sleep quality improvement</td>
</tr>
<tr>
<td>Matousek et al\textsuperscript{39}</td>
<td>Breast cancer patients</td>
<td>Reduction of stress levels, depression, anxiety and pain</td>
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<tr>
<td>Duncan et al\textsuperscript{40}</td>
<td>Breast cancer patients</td>
<td>Improvement of QoL and reduction of cortisol levels</td>
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controlled trial\textsuperscript{37} with cancer survivors concluded that 4 and 12 weeks of the MBSR program could reduce systemic cortisol levels by promoting a pro-immune phenotype in these patients. Another pilot study\textsuperscript{38} on fifty-seven cancer survivors with sleep disturbance described that MBSR is able to reduce cortisol levels slightly and improve sleep quality. Another study\textsuperscript{39} in breast cancer patients demonstrated short-term effects of the MBSR program (three days); in brief, MBSR improved self-reported stress levels, depression, and some clinical symptoms, including anxiety and pain. A study\textsuperscript{40} in prostate and breast cancer patients indicated that eight weeks of MBSR improved QoL and decreased stress symptoms, as well as reduced cortisol levels (Table I).

**Mean Clinical Outcomes of Mindfulness-Based Stress Reduction Interventions in Cancer Patients**

Mindfulness meditation interventions (MMBI) derived from MBSR techniques developed by Kabat-Zinn et al\textsuperscript{41} in 1979. As summarized in Table II, the first clinical uses of MBSR were performed in debilitating patients with chronic pain and aimed to improve cognitive functions and reduce stress\textsuperscript{41}. A pilot study\textsuperscript{42} evaluated that MMBI is able to reduce cortisol levels and anxiety in advanced-stage cancer patients and also to improve QoL and quality of work in clinicians. A randomized controlled trial\textsuperscript{43} in breast cancer patients assessed if MBSR could improve inflammation biomarker profile and immune functions. In detail, MBSR activates T cells through mitogen phytohemagglutinin and increases the Th1/Th2 ratio with a substantial recovery of B and Natural Killer cells, after cancer treatments\textsuperscript{43}. The overall picture of the study indicates that MBSR could be able to change immune functions in patients with cancer and push attention to randomized trials in patients treated with Immune Checkpoint Inhibitors (ICIs)\textsuperscript{43}.

A study\textsuperscript{44} on prostate and breast cancer patients indicates that twelve months of MBSR was effective in improving overall symptoms of stress as well as in reducing cortisol levels. Notably, Th1-related cytokines (with pro-inflammatory effects) and systolic blood pressure were strongly reduced in the MBSR group than in untreated patients, indicating anti-inflammatory and potential cardioprotective properties of MBSR in these patients\textsuperscript{44} (Table II). A study\textsuperscript{45} demonstrated that MBSR-based treatment improved symptoms of menopause and sleep quality in breast cancer patients. Another study\textsuperscript{46} in patients with breast

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<tbody>
<tr>
<td>Lengacher et al\textsuperscript{42}</td>
<td>Advanced stage cancer patients</td>
<td>Reduction in cortisol levels, improvement in QoL and fatigue</td>
</tr>
<tr>
<td>Lengacher et al\textsuperscript{43}</td>
<td>Breast cancer patients</td>
<td>Improvement of immune functions: increases in Th1/Th2 ratio; significant recovery of B and Natural Killer cells</td>
</tr>
<tr>
<td>Carlson et al\textsuperscript{44}</td>
<td>Prostate and breast cancer patients</td>
<td>Improvement of stress; reduction in cortisol levels. Th1-related cytokines and systolic blood pressure were strongly reduced</td>
</tr>
<tr>
<td>Chang et al\textsuperscript{46}</td>
<td>Breast cancer patients</td>
<td>Improvement in QoL, symptoms of menopause and sleep quality</td>
</tr>
<tr>
<td>Wu et al\textsuperscript{46}</td>
<td>Breast cancer patients</td>
<td>Stress reduction, improvement in QoL and reduction of cancer-related fatigue</td>
</tr>
<tr>
<td>Lengacher et al\textsuperscript{47}</td>
<td>Breast cancer patients</td>
<td>Reduction of IL-6 and cortisol levels</td>
</tr>
<tr>
<td>Zou et al\textsuperscript{48}</td>
<td>Cancer survivors</td>
<td>Reduction of blood pressure</td>
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<tr>
<td>Halal et al\textsuperscript{49}</td>
<td>Patients with heart failure</td>
<td>Reduction of hospitalization risk</td>
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<tr>
<td>Zou et al\textsuperscript{50}</td>
<td>Patients with heart failure</td>
<td>Reduction of depression, anxiety and heart rate</td>
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<tr>
<td>Tulloh et al\textsuperscript{51}</td>
<td>Patients with pulmonary arterial hypertension</td>
<td>Reduction of blood pressure and improvement of QoL</td>
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<tr>
<td>Joseph\textsuperscript{52}</td>
<td>Patients with hypertension as well as chronic heart failure</td>
<td>Reduction of systolic and diastolic blood pressure</td>
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<tr>
<td>Norman et al\textsuperscript{53}</td>
<td>Patients with chronic heart failure</td>
<td>Improvement of self-reported symptoms</td>
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<tr>
<td>Sullivan et al\textsuperscript{54}</td>
<td>Patients with chronic heart failure</td>
<td>Reduction of anxiety and depression</td>
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cancer concluded that MBSR relieved psychological stress, reduced anxiety, and depression, and improved sleep quality, positioning itself as a non-pharmacological strategy effective to improve QoL in patients with cancer. A study\textsuperscript{47} on 322 breast cancer patients demonstrated that six-week MBSR reduced cortisol and IL-6 levels. Cortisol levels were reduced immediately after the MBSR compared to baseline values; IL-6 changes had a similar behavior compared to cortisol, indicating the anti-inflammatory effects of MBSR in these patients\textsuperscript{47}.

**Cardiovascular Outcomes of Mindfulness-Based Stress Reduction Interventions**

As summarized in Figure 2, the MBSR program exerts some beneficial effects on patients with/without cancer. Among the improvement of QoL, stress, and reduction of cortisol levels in these patients, MBSR could be able to reduce cardiovascular risk factors. To date, few randomized clinical trials\textsuperscript{48} have focused on the cardiovascular outcomes of MBSR, and none in the cancer patient cohort (Table II). However, some recent studies\textsuperscript{48,49} indicate that MBSR could be beneficial to manage hypertension, and dyspnoea in chronic heart failure, and to reducing risk factors related to coronary heart disease, stroke, heart failure, aortic aneurysm, peripheral artery disease, and vascular dementia. A study\textsuperscript{48} demonstrated that two months of MBSR is able to reduce blood pressure (systolic blood pressure decreased by 16 mmHg and diastolic blood pressure decreased by around 4 mmHg; \(p<0.005\)). A recent study\textsuperscript{49} described that MBSR improved depression and QoL in patients with heart failure, and reduced hospitalization risk compared to untreated patients; however, the number of patients enrolled in this study is still to be improved, and large randomized controlled trials are needed to confirm these results. Another recent study\textsuperscript{50} summarized that MBSR could be beneficial in patients with heart failure, by reducing depression, anxiety, and heart rate, however, also in this study, authors concluded that more controlled and rigorous studies are needed. An interesting study\textsuperscript{51} aimed to verify the feasibility and the potential benefits of the MBSR program in patients with pulmonary arterial hypertension (PAH), considering its impact on reducing blood pressure and improving QoL. Authors\textsuperscript{51,52} concluded that attendance at group MBSR was poor in people with chronic PAH;

**Figure 2.** Main clinical outcomes of MBSR program in cancer patients. MBSR is able to reduce cortisol levels that consequently inhibit the synthesis of pro-inflammatory cytokines, e.g., IL-6 and IL-1. Cortisol reduction improves stress and QoL in these patients. The overall picture of the MBSR effects results in the enhancement of immune functions and reduction of cardiovascular and cancer-related risk factors.
Mindfulness-based interventions in cancer patients

therefore, a proper MBSR program (in situ or through online programs) should be performed in these patients. Another study\(^5\) demonstrated that MBSR significantly increases cardiac-vagal baroreflex sensitivity and heart-rate variability. These effects result in a significant reduction of systolic and diastolic blood pressure also in patients with hypertension as well as chronic heart failure\(^5\).

In summary, MBSR could be cardioprotective due to its stimulation of the vagal system that reduces systemic inflammation through cholinergic anti-inflammatory pathways\(^6\) (Table II) Another study\(^5\) in stable but symptomatic outpatients with chronic heart failure, concluded that MBSR alleviated self-reported symptoms in addition to conventional treatment. However, the sample size is small in this study\(^5\), and further studies are needed, but findings support the role of MBSR as a feasible method to reduce symptom burden in patients diagnosed with chronic heart failure. Another clinical trial\(^5\) reported that eight weeks of MBSR reduced anxiety and depression in patients with chronic heart failure. Notably, MBSR improves symptoms of chronic heart failure after one year of treatment\(^5\).

Conclusions

Randomized clinical trials available in the literature evidenced the beneficial effects of MBSR on the immune and metabolic functions of cancer patients, providing key insights into the closest collaboration between psycho-oncologists, oncologists, and cardiologists. As insight is gained into the clinical outcomes associated with MBSR methods, we propose MBSR as a complementary and alternative medicine warranting rapid investigation in patients with cancer, highlighting potential pro-immune and systemic anti-inflammatory outcomes.

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Authors’ Contributions

DB and NM conceived the manuscript, supervised the report and research, checked and validated the manuscript; VA, IB, OM and DDB contributed to the elaboration of literature and data; EQ, GM and MP supervised the paper; PF and VQ wrote, checked, revised and submitted the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Availability of Data and Materials

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

ORCID ID

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Mindfulness-based interventions in cancer patients


