Complementary Approaches for Military Women with Chronic Pelvic Pain: A Randomized Trial

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Abstract

Introduction: Active-duty (AD) women suffer with chronic pelvic pain (CPP) while providers tackle diagnoses and treatments to keep them functional without contributing to the opioid epidemic. The purpose of this study was to determine the effectiveness of non-invasive, self-explanatory mindfulness-based stress reduction (MBSR) or self-paced healthy lifestyle (HL) interventions on CPP in AD women.

Methods: We conducted a six-week interventional prospective study with AD women aged 21–55 at Mountain Home (MTHM), Idaho. Women were randomly assigned to MBSR (N = 21) or HL (N = 20) interventions. The primary outcome was pain perception. Secondary outcomes were depression and circulating cytokine levels.

Results: Women in the MBSR group exhibited reduced pain interference ($P < .01$) and depression ($P < .05$) alongside decreased IL-4 ($P < .05$), IL-6 ($P < .05$), eotaxin ($P < .05$), MCP-1 ($P = .06$), and IL-1ra ($P < .01$) and increased VEGF ($P < .05$). Those in the HL group did not have changes in pain, however, did exhibit reduced depression ($P < .05$) alongside decreased GM-CSF ($P < .05$) and increased TNF α ($P < .05$), SDF-1 ($P < .01$), and IL-1ra ($P < .01$).

Conclusion: AD women receiving MBSR or HL had reduced depression scores and altered circulating cytokine levels, however only those receiving MBSR had reduced pain perception. Findings support MBSR as an effective and viable behavioral treatment for AD women suffering from CPP.

Introduction

Chronic pelvic pain (CPP) was defined as noncyclic pain in the lower abdomen, back, or buttocks which is severe enough to require medical attention and is present for at least six months without successful treatment and expected to be lifelong¹ as this research was concluded prior to ACOG revising the CPP definition in March 2020. CPP is common, affecting 15% of the US population.² CPP can be disabling and causes distress on women's quality of life (QOL) including physical functioning, psychological well-being, and interpersonal relationships.² In addition, the condition is often elusive and difficult for providers to diagnose.^{2,3} Up to 55% of women continue to experience pain without obvious pathology even after surgical interventions.⁴ Frustrated with persistent symptoms and lack of improvement, these women stop seeking help.^{3,5}

As of July 2017, 15% of women were actively serving in the United States (US) military (<https://www.statisticbrain.com/women-in-the-military-statistics/>).⁶ These active duty (AD) women became combat deployable in 2016 after the US military officially lifted the ban on female soldiers serving in combat roles www.theguardian.com/world/2013/jan/24/us-military-lifts-ban-women-combat.⁷ While CPP in AD women has rarely been studied, one retrospective chart review reported 14% of female soldiers were seen for untreated pelvic pain during Operation Iraqi Freedom and Operation Enduring Freedom.⁸ Compared to civilians, AD women are at greater risk for hysterectomy for their CPP, and for hysterectomy at an earlier age (35 vs 43 yrs, $P < .0001$).⁹ Female veterans disproportionately suffer from CPP at an estimated prevalence of 30% and are more likely than male veterans to receive opioids for this pain.^{10,11} This is concerning with the epidemic of opioid use disorders affecting an estimated 2 million Americans and the rate increasing not only in the civilian population but also among AD service members and veterans (SAMHSA, 2019).^{12,13} Generally, women with CPP report a 45% rate of reduced productivity,¹⁴ a deficit detrimental in a combat zone. Due to co-morbidities associated with pain syndromes and mental health illness, it is recommended to screen for psychiatric disorders in any female veteran with unexplained pain.¹⁵ Lieutenant General Thomas Travis, the Surgeon General (SG) of the United States Air Force (USAF) in 2014, addressed the Subcommittee

on the Defense of the Health Programs in the military stating our main goal was to maintain a ready force and our quadruple aim was “Readiness, better health, better care, and best value.” The recent SG, Lieutenant General Dorothy Hogg, made this recommendation interminable. The American Congress of Obstetricians and Gynecologists (ACOG) considered awareness of female veterans’ unique health care needs as essential to practice in obstetrics and gynecology nationwide.¹⁶ It is imperative that we identify treatment approaches that are safe and effective for AD women with CPP.

The US Veterans Health Administration (VA) supports a biopsychosocial model assuming pain is influenced by a variety of different physical, pathological, psychological, social, and environmental factors.¹⁵ Female veterans with CPP screened positive for comorbid mood disorders at a rate of 31%, had lower healthy physical functioning scores, more medical symptoms, and higher numbers of days in bed because of illness at the VA.^{15,17} A large body of work suggests a role for pro-inflammatory cytokines in the pathophysiology of CPP,^{18–21} perceived stress and mood disorders (depression)²⁰ that often accompany CPP.

Alternative non-pharmacologic treatments such as mindfulness-based stress reduction (MBSR) or healthy lifestyle (HL) modifications including diet and exercise have been shown to reduce pro-inflammatory cytokine levels^{22,23} and are recommended for CPP.²⁴ These alternative treatments can lead to positive reappraisal, decrease biological stress pathways, and lower nociceptive excitability, thus breaking the self-sustaining cycle of pain and neurogenic inflammation.²⁵ However, these interventions have yet to be studied in the context of CPP in AD women. Thus, the purpose of the present study was to investigate the putative beneficial effects of non-invasive MBSR and HL interventions in AD women with CPP.

Materials And Methods

This interventional prospective study was approved by the University of Missouri-Kansas City Institutional Review Board, the TriService Nursing Research Program Human Research Protection Office (HRPO), and the Wilford Hall HRPO office. All research was performed in accordance with relevant guidelines and regulations provided by these governing bodies and informed consent was obtained from all participants. Records of participant participation followed regulatory guidance including Federal Privacy Act, 5 USC 522a and its implementing regulations, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and 45 CFR Parts 160 and 164. Additionally, all regulatory criteria met an additional ethics review at the MTHM AFB to assure proper protocol was adhered to with minimal concern for coercion. This study was registered with the grant in clinicaltrials.gov NCT04104542 (09/26/2019) and was designed to compare pain perception (intensity and interference) primarily, and secondarily depression and inflammatory cytokine biomarkers in AD women with CPP after a 6-week online MBSR or HL program.

Participants were recruited from outpatient clinics in an USAF military treatment facility (MTF) at Mountain Home (MTHM) Air Force Base, Idaho. The MTF at MTHM has family practice, mental health, and women’s health specialists who were able to assist with recruitment. The AD female population in Idaho includes Asian (N = 140 or 8.9%), Black (N = 59 or 3.7%), Hispanic (N = 146 or 9.3%), Mixed (N = 94 or 6%), White (N = 1128 or 72%).

Active-duty women with CPP, pain in the lower abdomen/back for greater than six months, were recruited through the Wilford Hall HRPO and the TriService Nursing Research Program HRPO at MTHM from June to August 2019 after assuring for participant protection. A preliminary eligibility assessment of interested participants was conducted via a telephone interview. A positive response to any of the following criteria in the initial interview led to exclusion: 1) age

< 21 or age > 50; 2) menopausal, pregnant, or breastfeeding; 3) pelvic/abdominal surgery within 6 months; 4) vaginal/pelvic infection at time of enrollment (as potential confounder of cytokines drawn), underlying diseases (cancer, diabetes, autoimmune); 5) unavailable to commit three months to study; 6) no access to computer or able to get online. Initially, the list of participants came from the group practice managers (GPM) and local women's health and family practice providers who agreed to help with recruitment of women with specific ICD 10 codes from their practice. A few women self-identified directly from flyers and a poster used for recruitment and all participants approved the primary investigator access to record review to confirm diagnosis.

Once consent was signed and diagnosis confirmed, participants were asked to complete valid and reliable questionnaires including a demographics questionnaire, a pain questionnaire (the Brief Pain Inventory-BPI), a depression questionnaire (the Patient Health Questionnaire – PHQ9), and a mindfulness questionnaire (the Five Facets of Mindfulness – FFMQ), sent through the Research Electronic Data Capture (REDCap). Through REDCap, data was managed securely with an infrastructure programming allowing for the blinded assignment of these AD women with CPP to either the MBSR or the HL interventions. Once assigned, only the PI had oversight to manage the database.

MBSR, a complementary treatment with an emphasis on cultivating a focused, contemplative self-awareness, can help patients obtain self-regulation for health improvement in positive reappraisal coping.²⁶ The classic in-person MBSR class is the best way to learn mindfulness because of live interaction and group support, but is not always feasible. For this study, MBSR online-training consisted of classic journal and written guidance with YouTube videos found on palousemindfulness.com with weekly homework assignments, progress reports, and readings each woman could perform asynchronously for convenience. There was access to online support trainings for still and moving meditations. Each participant had access to a step-by-step guide on chapters to read from “Full Catastrophe Living” by Jon Kabat-Zin each week, the asynchronous daily mindfulness sessions, a journal, and an online guide from Dave Potter. Weekly readings and videos included a different focus. This group was required to set aside 30-minutes five-days weekly for their “homework” to remain in the study. The PI had no access of these trainings and relied on the participants acknowledgement of homework assignments. Week *one* focused on simple awareness, an introduction to the body scan, which is tuning in to the body and reconnecting to the physical self. Week *two* began sitting meditation. Week *three* introduced yoga and dealing with thoughts and distractions. Week *four* focused on one-minute breathing space, responding vs reacting. Week *five* focused on turning toward the difficulty instead of moving away from it. Week *six* focused on mountain and lake meditations and the sacred art of listening. Questionnaires were completed and lab samples collected at six-weeks.

The HL group had access to weekly voice-over slides that guided them in nutrition and exercise choices with a different focus each week. It was modeled after the Group Lifestyle Balance (GLB) course found at USAF bases used by Nutritional Medicine to work with patients with diabetes or weight concerns. This group was required to journal at least five-days weekly entering their workouts and meals with a specific target goal to meet by the end of the study. The PI was able to monitor daily journaling in the fitness tracker and send weekly reminders. Week *one* introduced the program, the free fitness tracker application recommendation ([myfitnesspal](http://myfitnesspal.com)), and basic nutrition. Week *two* included slides that encouraged participants to focus on their goals with nutrition tips to help them meet their targets. Week *three* reviewed participant goals while offering suggestions for selecting foods while shopping. Week *four* focused on fitness goals and training motivation. Week *five* discussed interactive work calculation of “typical meals” for dining out at different restaurants. Week *six* reviewed strength training, progress, diaries, goals pending and met. Each member documented in [myfitnesspal](http://myfitnesspal.com) and shared their diary with one of the authors (CDC). This free site helped the HL participant journal their diet and exercise daily and track their goals.

All AD members have access to a certified nutritionist trained in telephone coaching and these women were informed that this was still available if desired to help guide them. Many of the HL group were advised to use the fermentable oligo-, di-, mono-saccharides and polyols, or FODMAP diet due to their specific type of CPP. All slides were forwarded to the HL participants and they could elect to watch them asynchronously, when it was convenient allowing for varying schedules.

Mindfulness was measured among participants in both the MBSR and HL groups. To measure mindfulness, a multifaceted construct characterized by a shift in attention resulting in observation of each moment experience without interpretation, elaboration, or analysis of that experience as an intentional and non-judgmental awareness, the FFMQ was used.²⁷ The FFMQ consists of subscales that measure the five facets of mindfulness: observe, describe, act with awareness, nonreactivity, and nonjudging, with 39-statements on a 5-point Likert-type scale ranging from one to five.²⁷ Facet scores range from 8–40, except for the nonreactivity facet, which ranges from 7–35.

Pain Perception (intensity and interference) were measured using the Brief Pain Inventory (BPI). The intensity of pain is measured by 4-items, (current as well as worst, least, and average in the past week) on 0 “no pain” to 10 “worst pain imagined” for the numerical scales. Seven activities describe the interference and include (general activity, mood, walking, work, relations with others, sleep, and enjoyment of life) where 0 refers to “no interference” and 10 “complete interference”.²⁸ It is used in the military and can be completed in less than 5-minutes. It has established reliability (Cronbach’s alpha ranges: 0.77 to 0.91), internal consistency, good to excellent test-retest values (ICC .84-.90) and construct validity $\alpha > .70$ in seven of nine studies documenting pain in cancer patients, lower back pain, range of motion, muscle tenderness.²⁸

Depression was measured using the Patient Health Questionnaire (PHQ9), a 9-item Likert-type self-assessment nominal screening and diagnostic tool used in primary care clinics in the Department of Defense (DOD) and VA routinely for somatic symptoms in depression. The PHQ-9 scores each item from 0 to 3 providing a severity score ranging between 0 and 27. The scores 0, 1, 2, and 3 are assigned to the response categories referring to frequency of a particular symptom over the last two weeks with “not at all”, “several days”, “more than half the days”, and “nearly every day” respectively.²⁹ The severity of depression scores is graded as none/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). The PHQ9 has a sensitivity of 51% and a specificity of 94%, high validity (AUROC 0.85, 95% CI 0.82–0.88).²⁹ The PHQ-9 has been used internationally as a criterion-based diagnosis of mental disorders translated in 25 languages with adequate reliability, and construct and criterion validity in diverse samples. The DOD used the PHQ-9 in veterans and found adequate internal consistency (Cronbach’s $\alpha = 0.92$, 95% CI = 1.86–19.13) and test-retest (0.84).³⁰

Blood draws were not standardized by time of day or menstrual cycles due to the limited time of day available for laboratory access for participants and the PI. Cytokine concentrations in plasma were measured using a multiplex electrochemiluminescence immunoassay kit developed by Meso Scale Discovery (MSD). The customized U-PLEX (Cat. #K15054D) assay consisted of the following analytes: GM-CSF, IFN γ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-17A, TNF α , IL-1RA, MCP-1, SDF-1, and VEGF α . The assay was carried out according to the manufacturer’s instructions. Frozen plasma samples were thawed on ice then diluted fourfold, run in duplicate, and analyzed using Discovery Workbench 4.0.12 software (MSD). Calibrators supplied by MSD were used to create standard curves and extrapolate sample concentration.

The collected data stored on REDCap was transferred to R version 3.5.0 for statistical analyses. Next, data was described using standard statistical methods such as frequency distribution, graphical displays of data, and application of the appropriate descriptive statistics to determine each variable’s central tendency, distribution, and

variability. Descriptive statistics were provided for subject characteristics and can be found in Table 1 provided. Categorical variables are reported with counts and percentages, while continuous variables are reported as medians and interquartile ranges. The primary outcome was considered change in scores on the BPI and secondarily, change in scores for FFMQ and PHQ-9 questionnaires. An a priori power analysis found that a sample size of N = 100 would be required to achieve a statistical power of 0.8, for an alpha level of 0.05 and an effect size of 0.5. Though underpowered with a sample size of N = 27, we maintained an alpha level of 0.05 to determine an effect size of 0.5 which is considered moderate to large.

The Mann-Whitney U (Wilcoxon signed rank) test was used to compare the distribution of values for each group determine differences between groups at baseline pre-intervention as well as within group differences for changes (pre- to post-intervention) in mindfulness facets, pain scores, depression scores, and cytokine levels. Statistical significance was defined as $P < .05$. Due to the exploratory nature of cytokine analyses, no adjustment was made for multiple comparisons.

Results

The analysis included 41 eligible evaluable participants (MBSR=21, HL=20) from MTHM. A high attrition was projected for the “online” treatments, but the last-minute deployment contributed to even higher attrition (30% versus 10%) for personal or professional obligations. The final completion total for both groups was N=28, including 14 participants for each group with 12 HL serum samples and 13 MBSR serum samples. Furthermore, participants subjected to deployments (two from the HL and seven from the MBSR group) necessitated a shortened study for a post assessment (T2) at six-weeks instead of the initial projected eight-weeks. There were no significant differences found within the demographics between groups as seen in Table 1.

Table 1 Demographics

	HL (n=12)	MBSR (n=13)	P-value
Age			0.290
21-26	3 (25.0%)	4 (30.8%)	
27-32	2 (16.7%)	6 (46.2%)	
33-38	1 (8.3%)	1 (7.7%)	
39-44	5 (41.7%)	1 (7.7%)	
45-50	1 (8.3%)	1 (7.7%)	
Race			0.888
Black	1 (8.3%)	3 (23.1%)	
Caucasian	9 (75.0%)	8 (61.5%)	
Mixed	1 (8.3%)	1 (7.7%)	
Other	1 (8.3%)	1 (7.7%)	
Education History			0.294
GED or High School	1 (8.3%)	3 (23.1%)	
Associate's Degree	9 (75.0%)	5 (38.5%)	
Bachelor's Degree	2 (16.7%)	4 (30.8%)	
Master's Degree	0 (0%)	1 (7.7%)	
Marital Status			>0.999
Single	3 (25.0%)	3 (23.1%)	
Married	8 (66.7%)	9 (69.2%)	
Divorced	1 (8.3%)	1 (7.7%)	
Use of Contraception			0.056
Oral Contraceptive	4 (33.3%)	2 (15.4%)	
Intrauterine Device	1 (8.3%)	1 (7.7%)	
Injectable Hormone	1 (8.3%)	0 (0%)	
Sterilization	4 (33.3%)	1 (7.7%)	
None	2 (16.7%)	9 (69.2%)	
Number of Pregnancies			0.127
None	4 (33.3%)	8 (61.5%)	
1-2	4 (33.3%)	4 (30.8%)	
3	3 (25.0%)	0 (0%)	
>3	1 (8.3%)	1 (7.7%)	

Live Births		0.067
None	5 (41.7%)	8 (61.5%)
1-2	5 (41.7%)	4 (30.8%)
3	2 (16.7%)	1 (7.7%)
Cesarean Deliveries		0.587
None	11 (91.7%)	9 (69.2%)
1-2	0 (0%)	3 (23.1%)
Caffeine (servings per day)		0.246
1	0 (0%)	2 (15.4%)
2	3 (25.0%)	6 (46.2%)
3	8 (66.7%)	4 (30.8%)
>3	1 (8.3%)	1 (7.7%)
Nicotine Use		0.480
None	10 (83.3%)	11 (84.6%)
< ½ pack per day	1 (8.3%)	0 (0%)
½-1 pack per day	1 (8.3%)	0 (0%)
Vaping Daily	0 (0%)	2 (15.4%)
Alcoholic Beverages (per week)		0.017
None	3 (25.0%)	7 (53.8%)
1-3	9 (75.0%)	3 (23.1%)
4-6	0 (0%)	3 (23.1%)
Weekly Exercise (minutes)		0.713
30-60 minutes	1 (8.3%)	4 (30.8%)
61-75 minutes	2 (16.7%)	2 (15.4%)
> 75 minutes	9 (75.0%)	7 (53.8%)

Pre-intervention comparisons with the FFMQ showed no significant differences between groups. However, post-intervention comparisons demonstrated significant improvements for the MBSR group for all mindfulness facets except *describe*. No significant changes in mindfulness were found for the HL group. This demonstrated fidelity for the MBSR group along with assuring the HL group was still “novice” to MBSR by comparison.

We next evaluated the effectiveness of MBSR and HL on pain. Of the 28 participants who completed the study, 27 completed the BPI at both time points. There were no significant differences in BPI scores between MBSR and HL groups pre-intervention and no group differences observed in pain intensity at six-weeks post-intervention. However, at six-weeks post-intervention, women in the MBSR group exhibited significant reductions in pain interference ($P < .01$,

95% CI for median decrease in pain score [-3.0, -1.0]), over time, while those in the HL group did not ($P \leq .51$, 95% CI for median decrease in pain score [-3.0- 2.0]). See Figure 1.

We next evaluated the effectiveness of MBSR and HL on depression scores. All nine-questions were individually confirmed within each group with paired samples correlations. No significant differences in PHQ-9 scores were observed between MBSR and HL groups pre-intervention. Women in both the MBSR ($P < .05$, 95% CI for median decrease in depression score [-4.0- 0.0]) and HL ($P < .05$, 95% CI for median decrease in depression score [-2.0- 0.0]) groups had an overall significant reduction in depression score over time measured with the Total PHQ9. See Fig. 2.

Finally, we evaluated the effects of MBSR and HL on plasma levels of pro- and anti-inflammatory cytokines. As shown in Figure 3, the MBSR group had decreased levels of interleukin-4 (IL-4; $P < .05$, 95% CI [-0.28- .76]), interleukin-6 (IL-6; $P < .05$, 95% CI [.21- 1.31]), eotaxin ($P < .05$, 95% CI [-1.46- 319.8]), monocyte chemoattractant protein-1 (MCP-1; $P = .06$, 95% CI [-16.82- 228.7]), and interleukin-1 receptor antagonist (IL-1ra; $P < .01$, 95% CI [-5.85- 156.1]) with increased levels of vascular endothelial growth factor (VEGF; $P < .05$, 95% CI [-80.49- 7.88]) over time (pre- to post-intervention) measured. As shown in Figure 4, the HL group had decreased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF; $P < .05$, 95% CI [0.0- 0.87]) and increased levels of tumor necrosis alpha (TNF α ; $P < .05$, 95% CI [-9.65- 0.0]), stromal cell-derived factor 1 (SDF-1; $P < .01$, 95% CI [-1039- -193.1]), and IL-1ra ($P < .01$, 95% CI [-147.1- -57.71]).

Discussion

This study was designed to evaluate the effectiveness of a non-invasive, self-explanatory MBSR or self-paced HL intervention primarily on CPP. Additionally, co-morbid depression, and inflammation among AD women were assessed. We found that AD women receiving a 6-week MBSR intervention had significant reductions in CPP. Further, women receiving either the MBSR or HL interventions had significant reductions in depression alongside changes in plasma cytokine levels. While prior research has found MBSR and HL interventions effective for the management of CPP and related pain and health conditions, our results are the first to demonstrate the benefit of MBSR and HL in a population of AD women with CPP.

The MBSR training significantly improved mindful actions for the MBSR group with a 24% reduction in pain interference scores and a 15% reduction in depression scores post-intervention. This finding is in line with published reports demonstrating that MBSR training improves pain and depression among patients with CPP.^{22, 31, 32}

Women in the MBSR group also exhibited significant changes in cytokine expression levels. Specifically, levels of IL-4, IL-6, eotaxin, MCP-1, and IL-1ra were decreased and levels of VEGF were increased. Cytokines are small intracellular regulatory proteins secreted by immune cells in the periphery and neurons and glia in the central nervous system.²¹ Pro-inflammatory cytokines increase the activity of nociceptors by direct receptor-mediated actions as well as by inducing the transcription of pain-relevant genes that promote long-term synaptic plasticity.¹⁸ Meanwhile, anti-inflammatory cytokines negatively regulate pro-inflammatory cytokine expression and signaling to resolve inflammation and reduce pain.³³ IL-6, eotaxin, and MCP-1 are pro-inflammatory cytokines whose levels are elevated in patients with CPP³⁴⁻³⁶ such that higher levels are associated with greater pain.³⁷ Additionally, elevated levels of these cytokines are correlated with depressed mood^{38, 39} which often accompanies CPP. The finding that expression levels of these cytokines were reduced following the MBSR intervention suggests that mindfulness may reduce pain and improve mood through normalizing cytokine signaling.

IL-4 and IL-1ra are anti-inflammatory cytokines well-known to have analgesic effects,³³ and MBSR interventions that improve QOL, mood, and stress have been shown to increase their levels.⁴⁰ Thus, the finding that IL-4 and IL-1ra levels were decreased following MBSR was surprising, although in line with data from a study where plasma levels of IL-4 were elevated in endometriosis patients.⁴¹ The finding that VEGF levels were increased following MBSR was also unexpected, as VEGF regulates angiogenesis and pain⁴² and increased levels have been observed in patients with CPP.⁴³ Notably, the resolution of inflammation is an active process characterized by cyclical fluctuations in cytokines and growth factors released by immune and other cells to regain physiological homeostasis.⁴⁴ Thus, measurement of cytokines at multiple time points following MBSR may be required to understand the impact of this intervention on regulating pro- versus anti-inflammatory cytokines throughout this process.

While women in the HL group did not have significant reductions in pain scores, they did exhibit a 12% reduction in depression scores at the completion of the intervention. This finding is like others demonstrating the positive impact of HL interventions on mood. Specifically, a diet high in fruits, vegetables, whole grains, and antioxidants and low intake of animal foods has been associated with a decreased risk of depression.⁴⁵ Additional evidence demonstrates that exercise reduces depressive symptoms and improves QOL and physical function, independent of factors such as education or physical health.^{46,47} The HL women also exhibited significant changes in cytokine expression levels. Specifically, levels of GM-CSF decreased and levels of TNF α , SDF-1, and IL-1ra increased. GM-CSF is an important hematopoietic factor that can promote macrophage migration from the bone marrow, contributing to the inflammatory process observed in depressive disorders.⁴⁸ Anti-depressants, such as fluoxetine, have been found to reduce plasma levels of GM-CSF associated with improved mood.^{48,49} IL-1ra is a member of the IL-1 cytokine family that serves as an endogenous negative-feedback regulator to control potentially pathologic inflammatory events.⁵⁰ In addition to alleviating pain, IL-1ra improves mood in patients with depression and has been an important therapeutic target.⁵⁰ Thus, HL training may improve mood in women with CPP through normalizing GM-CSF and IL-1ra signaling.

We also observed intervention-dependent increases in levels of the pro-inflammatory cytokines TNF α and SDF-1. TNF α is a key regulator of immune function implicated in numerous health problems of immune origin including CPP⁵¹ and depression.⁵² SDF-1 is emerging as an important contributor to pelvic inflammatory diseases⁵³ and depressive mood disorders.⁵⁴ Long-lasting increases in TNF α and SDF-1 are maladaptive, however transient increases following HL interventions like exercise may be vital for adaptive responses to training that ultimately have beneficial effects on mood. Acute release of TNF α after exercise is necessary to induce anti-inflammatory cytokines (eg, IL-1ra) promoting resolution of inflammation, tissue repair, and improved mood.⁵⁵ Acute increases in SDF-1 following exercise training augment the function of myocytes⁵⁶ leading to regeneration of skeletal muscle and vascular tissues, respectively. While there is a gap in our understanding of specific mechanisms whereby combined exercise and nutrition training improve depression, our findings together with published results suggest that a HL stimulates immune, muscle, and other cells to secrete pro- and anti-inflammatory cytokines influencing mood-relevant pathways.

The online MBSR and HL interventions allowed for self-care in a military setting with widest dissemination for training at the participant's own time. Using a web-based survey had several advantages including population accessibility, time savings, and reduced cost. Online resources can potentially reach more AD members. Professional demands in the military can be overwhelming for many and having a resource that is easily accessible to them anywhere can be life changing. Active participation in an online MBSR program which otherwise would not have been available, can potentially lead to less physiological reactivity in response to stressors, improving morbidity.

However, this study had several limitations. First, participants had to have access to emails and capability to open attached links. The sheer amount of survey requests using web-based systems to approach potential study participants invariably led to respondent fatigue and unwillingness to participate by some. Second, the sample size was small, increasing the chance of a type I error, and was restricted to MTHM, which may limit generalizability. Third, nutrition and exercise were not monitored for the MBSR group. Additionally, monitoring for major life events was not included.

Future research should include comparisons using alternative MBSR trainings (classic model versus online-only MBSR) along with monitoring training for HL activities. Furthermore, a larger study focusing on the combined effects of MBSR and HL with a control arm measuring results over an extended period (6 months) would help understand sustainability and continued impact of the interventions. Discovering interventions beneficial in improving coping with chronic pain is relevant and necessary to future studies.

In summary, both MBSR and HL represent safe, effective, and feasible treatment options for AD women with CPP. MBSR was superior in that it improved pain and related depression symptoms. Though HL did not have a significant effect on pain, it did reduce co-morbid depression and, thus, may have added benefit when used in combination with MBSR.

Declarations

Disclosures

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Author Contributions CDC designed the study, wrote the manuscript, prepared table. AN performed laboratory experiments, prepared figures, and wrote the manuscript. EA had oversight and contributed to the writing of the manuscript. RB and MF performed analysis and prepared the figures. All authors contributed to the interpretation of results and reviewed the contents of the manuscript.

References

1. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. *Obstet Gynecol*, **103** (3), 589–605 (2004).
2. Yosef, A. *et al.* Chronic pelvic pain: Pathogenesis and validated assessment. *Middle East Fertility Society Journal*, **21** (4), 205–222 <https://doi.org/10.1016/j.mefs.2016.08.001> (2016).

3. Ayorinde, A. A., Bhattacharya, S., Druce, K. L. & Jones, G. T. Chronic pelvic pain in women of reproductive and post-reproductive age: a population-based study. *Euro J Pain*. 21(3),445–455; 10.1002/ejp.938 (2017).
4. Al-Abbadey, M., Liossi, C., Curran, N. & Schoth, D. E. Treatment of female sexual pain disorders: A systematic review. *J Sex & Marital Therapy*.42(2),99–142; 10.1080/0092623X.2015 (2016).
5. Latthe, P., Mignini, L., Gray, R., Hills, R. & Khan, K. Factors predisposing women to chronic pelvic pain: Systematic review. *Br Med J*.332(7544),749–751; 10.1136/bmj.38748.697465.55 (2006).
6. Statistics for Military found at: <https://www.statisticbrain.com/women-in-the-military-statistics/> Accessed January 6, 2020
7. Harris, P. (2013, January 25). Women in combat: US military officially lifts ban on female soldiers. *The Guardian*. <https://www.theguardian.com/world/2013/jan/24/us-military-lifts-ban-women-combat>
8. Wright, J. Jr. *et al*. Pelvic pain presenting in a combat environment. *Mil Med*.171(9),841–843; 10.7205/MILMED.171.9.841 (2006).
9. Ryan, G. L. *et al*. Hysterectomy risk in premenopausal-aged military veterans: associations with sexual assault and gynecologic symptoms. *Am J Obstet & Gynecol*.214(3), 352.e351-352.e313; 10.1016/j.ajog.2015.10.003 (2016).
10. Cichowski, S. B. *et al*. Military Sexual Trauma in Female Veterans is Associated with Chronic Pain Conditions. *Mil Med*. 182(9–10), e1895-e1899; 10.7205/MILMED-D-16-00393 (2017).
11. Cichowski, S. B. *et al*. 10-yr analysis of chronic pelvic pain and chronic opioid therapy in the women veteran population. *Mil Med*.10.1093/milmed/usy114 (2018).
12. Vallerand, A. H., Cosler, P., Henningfield, J. E. & Galassini, P. Pain management strategies and lessons from the military: A narrative review. *Pain Res Manage*. 20(5),261–268. 10.1155/2015/1 (2015).
13. Substance Abuse and Mental Health Services Administration (2019). *Opioid treatment program directory*. Department of Health and Human Services. Retrieved from <https://dpt2.samhsa.gov/treatment/directory.aspx>
14. Mathias, S., Kuppermann, M., Liberman, R., Lipschutz, R. & Steege, J. Chronic Pelvic Pain: Prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol*.87(3),321–327; 10.1016/0029-7844(95)00458-0 (1996).
15. Higgins, D. M., Kerns, R. D., Brandt, C. A. & Haskell, S. G. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Veterans. *Pain Med*, 15 (5), 782–790 <https://doi.org/10.1111/pme.12388> (2014).
16. Committee on Health Care for Underserved Women. Committee opinion: health care for women in the military and women veterans. *Obstet Gynecol*.120:1538–1542. 10.1097/01.AOG.0000423821.70036.5a (2012).
17. Levander, X. A. & Overland, M. K. Care of women veterans. *Med Clin N Am*. 99(3), 651;10.1016/j.mcna.2015.01.013 (2015).
18. Gao, Y. J. *et al*. JNK-induced MCP-1 production in spinal cord astrocytes contributes to central sensitization and neuropathic pain. *J Neurosci*.29(13),4096–4108; 10.1523/JNEUROSCI.3623-08.2009 (2009).
19. Hoge, E. A. *et al*. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depr and Anx*.26(5),447–455; 10.1002/da.20564 (2009).
20. Maes, M. Major depression and activation of the inflammatory response system. *Adv Exper Med Bio*.461,25–46; 10.1007/978-0-585-37970-8\$42 (1999).
21. Miller, R. J., Jung, H., Bhango, S. K. & White, F. A. *Cytokine and Chemokine Reg Sens Neuro Function*. Handbook of Experimental Pharmacology. 10.1007/978-3-540-79090-7\$412 (2009).

22. Rosenkranz, M. A. *et al.* A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain, Behav, Immun.* 27(Supplement C), 174–184; 10.1016/j.bbi.2012.10.013 (2013).
23. Zhang, H. & Zhang, C. Vasoprotection by Dietary Supplements and Exercise: Role of TNF α Signaling. *Exp Diab Res.* 10.1155/2012/972679 (2012).
24. Chao, M. T. *et al.* Prevalence and use of complementary health approaches among women with chronic pelvic pain in a prospective cohort study. *Pain Med.* 16(2):328–340; 10.1111/pme.12585 (2015).
25. Garland, E., Gaylord, S. & Park, J. The role of Mindfulness in positive reappraisal. *Explore.* 5(1), 37–44; 10.1016/j.explore.2008.10.001 (2009).
26. Brotto, L. A. *et al.* A Comparison of Mindfulness-Based Cognitive Therapy Vs Cognitive Behavioral Therapy for the Treatment of Provoked Vestibulodynia in a Hospital Clinic Setting. *J Sex Med.* 16(6), 909–923. 10.1016/j.jsxm.2019.04.002 (2019)
27. Baer, R. A. *et al.* Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment.* 15(3), 329–342; 10.1177/1073191107313003 (2008).
28. Jelsness-Jørgensen, L-P. *et al.* Validity, Reliability, and Responsiveness of the Brief Pain Inventory in Inflammatory Bowel Disease. *Canad J Gastro Hepatol.* 1–10. 10.1155/2016/5624261 (2016).
29. Bhana, A., Rathod, S. D., Selohilwe, O., Kathree, T. & Petersen, I. The validity of the Patient Health Questionnaire for screening depression in chronic care patients in primary health care in South Africa. *BMC Psych.* 15, 118; 10.1186/s12888-015-0503-0 (2015).
30. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 16(9), 606–613; 10.1046/j.1525-1497.2001.016009606.x (2001).
31. Crisp, C. D., Hastings-Tolsma, M. & Jonscher, K. R. Mindfulness-Based Stress Reduction for military women with chronic pelvic pain: A feasibility study. *Mil Med.* 81(9), 982–989; 10.7205/milmed-d-15-00354 (2016).
32. Fox, S. D., Flynn, E. & Allen, R. Mindfulness meditation for women with chronic pelvic pain, a pilot study. *J Repro Med,* 56 (3–4), 158–162 (2011).
33. Zhang, J. M. & An, J. Cytokines, inflammation, and pain. *Int Anesthes Clin,* 45 (2), 27–37 <https://doi.org/10.1097/AIA.0b013e318034194e> (2007).
34. Gul, E. & Celik Kavak, E. Eotaxin levels in patients with primary dysmenorrhea. *J Pain Research.* 11, 611–613; 10.2147/JPR.S146603 (2018).
35. Liebrechts, T. *et al.* Immune activation in patients with irritable bowel syndrome. *Gastro,* 132 (3), 913–920 <https://doi.org/10.1053/j.gastro.2007.01.046> (2007).
36. Lindenlaub, T. & Sommer, C. Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. *Acta Neuropath,* 105 (6), 593–602 <https://doi.org/10.1007/s00401-003-0689-y> (2003).
37. Ogura, N. *et al.* MCP-1 production in temporomandibular joint inflammation. *J Dent Res,* 89 (10), 1117–1122 10.1177/0022034510376041 (2010).
38. Teixeira, A. L., Gama, C. S., Rocha, N. P. & Teixeira, M. M. Revisiting the Role of Eotaxin-1/CCL11 in Psychiatric Disorders. *Front Psych.* 9, 241; 10.3389/fpsy.2018.00241 (2018).
39. Leighton, S. P. *et al.* Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Molec Psych,* 23 (1), 48–58 <https://doi.org/10.1038/mp.2017.205> (2018).
40. Witek-Janusek, L. *et al.* Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain Behav Immun,* 22 (6), 969–981 (2008).

41. Drosdzol-Cop, A., Skrzypulec-Plinta, V. & Stojko, R. Serum and peritoneal fluid immunological markers in adolescent girls with chronic pelvic pain. *Obstet & Gynecol Survey*. 67(6),374–381; 10.1097/OGX.0b013e31825cb12b (2012).
42. Hulse, R. P. Role of VEGF-A in chronic pain. *Oncotarget*, 8 (7), 10775–10776 (2017).
43. Dagher, A. *et al.* Identification of novel non-invasive biomarkers of urinary chronic pelvic pain syndrome: findings from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. *BJU Int*.120(1):130–142. 10.137/journal.pone.0206807 (2017).
44. Ortega-Gómez, A., Perretti, M. & Soehnlein, O. Resolution of inflammation: an integrated view. *EMBO Mol Med*.5(5):661–674; 10.1002/emmm.201202382 (2013).
45. Li, Y. *et al.* Dietary patterns and depression risk: A meta-analysis. *Psych Res*.253,373–382. 10.1016/j.psychres.2017.04.020 (2017).
46. Geneen, L. J. *et al.* Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database of System Rev*.4; 10.1002/14651858.CD011279.pub3 (2017).
47. Song, M. R., Lee, Y. S., Baek, J. D. & Miller, M. Physical activity status in adults with depression in the National Health and Nutrition Examination Survey, 2005–2006. *Pub Health Nurs. (Boston, Mass.)*.29(3),208–217. 10.1111/j.1525-1446.2011.00986.x (2012).
48. Becerril-Villanueva, E. *et al.* Alterations in the Levels of Growth Factors in Adolescents with Major Depressive Disorder: A Longitudinal Study during the Treatment with Fluoxetine. *Med Inflamm*.9130868; 10.1155/2019/9130868 (2019).
49. Liu, J. J. *et al.* Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis. *Mol Psych*, 25 (2), 339–350 <https://doi.org/10.1038/s41380-019-0474-5> (2020).
50. Koo, J. W. & Duman, R. S. Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. *Curr Opin Invest Drugs*, 10 (7), 664–671 (2009).
51. Seckin-Alac, E., Akhant, S. E., Bastu, E., Tuzlalik, S. & Yavuz, E. Elevated tissue levels of tumor necrosis factor- α in vulvar vestibulitis syndrome. *Clin Exper Obstet & Gynecol*, 41 (6), 691–693 (2014).
52. Ma, K., Zhang, H. & Baloch, Z. Pathogenetic and Therapeutic Applications of Tumor Necrosis Factor- α (TNF- α) in Major Depressive Disorder: A Systematic Review. *Inter J Mol Scie*, 17 (5), 733 <https://doi.org/10.3390/ijms17050733> (2016).
53. Yang, S. F., Wu, T. F., Tsai, H. T., Lin, L. Y. & Wang, P. H. New markers in pelvic inflammatory disease. *Clinica chimica acta; Inter J Clin Chem*. 431,118–124; 10.1016/j.cca.2014.02.004 (2014).
54. Stuart, M. J., Singhal, G. & Baune, B. T. Systematic Review of the Neurobiological Relevance of Chemokines to Psychiatric Disorders. *Front Cell Neuro*. 9,357; 10.3389/fncel.2015.00357 (2015).
55. Sugimoto, M. A., Sousa, L. P., Pinho, V., Perretti, M. & Teixeira, M. M. Resolution of Inflammation: What Controls Its Onset?. *Front Immunolog*. 7,160; 10.3389/fimmu.2016.00160 (2016).
56. Puchert, M., Adams, V., Linke, A. & Engele, J. Evidence for the involvement of the CXCL12 system in the adaptation of skeletal muscles to physical exercise. *Cell Signal*, 28 (9), 1205–1215 <https://doi.org/10.1016/j.cellsig.2016.05.019> (2016).

Figures

Figure 1

Changes in Pain Scores Following MBSR or HL Interventions

Figure 2

Changes in Depression Scores Following MBSR or HL Interventions.

Figure 3

Changes in Cytokine Levels Following the MBSR Intervention.

Figure 4

Changes in Cytokine Levels Following the HL Intervention.

Supplementary Files

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- [Consort2010checklistComplementaryApproachesforMilitaryWomenwithChronicPelvicPainARandomizedTrial.doc](#)