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Effectiveness of Cognitive-Behavioral Stress Management on Distress Tolerance, Pain Perception and Interleukin-12 in MS Patients

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Abstract

Objective: This study aimed to investigate the effectiveness of Cognitive-Behavioral Stress Management (CBSM) therapy on distress tolerance, pain perception, and interleukin-12 (IL-12) in patients with Multiple Sclerosis (MS).
Method: The present study was a quasi-experimental design with pretest-posttest, follow-up, and control group. The statistical population included all female patients with relapsing-remitting MS who had been referred to Neuroscience and Rehabilitation Research Centers of Tehran Medical Sciences University. Among them, 20 patients were selected by convenience sampling and were randomly assigned to experimental (10 patients) and control groups (10 patients). The experimental group received the CBSM. Participants completed the research scales. To measure IL-12, the Enzyme-Linked Immunosorbent Assay (ELISA) was used. The data were analyzed using multivariate analysis of covariance (MANCOVA) and Bonferroni post-hoc test.
Results: CBSM increased the distress tolerance and components of pain perception (perceived influence of important people and doing daily affairs) ($p<0.001$) and decreased pain severity and IL-12. Also, these changes remained stable during follow-up.
Conclusions: CBSM is effective on distress tolerance, pain perception, and IL-12 in MS patients.

Keywords: Cognitive-Behavioral Stress Management, Distress Tolerance, Pain Perception, Interleukin-12, MS.

Introduction

Multiple Sclerosis (MS) is an inflammatory disorder of the central nervous system that destroys the myelin sheath in the brain and spinal cord. This disease is more common in young adults and women than in men. Multiple Sclerosis causes sensory disturbances (including numbness or paresthesia), impaired motor function (including weakness or paralysis), impaired vision (such as diplopia, blurred vision, and impaired coordination of eye movements), impaired bowel and bladder function, cognitive impairment, and fatigue (Joseph, 2019; Tarlinton et al., 2020), and mental disorders (Sparaco, Lavorgna, & Bonavita, 2019). Distress tolerance is one of the main variables in this disease (Sanagoei Mohrar & Hosseinzadeh, 2017) and, as an emotional feature, it refers to the capacity to experience and tolerate negative psychological states that may be the result of cognitive or physical processes that appears as an emotional state (Simons & Gaher, 2005). Individuals with MS have high levels of distress intolerance (Alschuler & Beier, 2015; Kafaki, Moafi, Golestani, Bekineh, & Ebrahimi, 2017; Heffer-Rahn & Fisher, 2018; Hayek et al., 2020). Pain as an unpleasant psychological and emotional experience (Melzack & Wall, 2016) is one of the

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most distressing symptoms of MS (Heitmann et al., 2020; Kim et al., 2020; Yusuf et al., 2020), which has received little attention in medical literature, but studies have shown that pain is a common symptom in these patients (Burkill et al., 2019). Also, Pain may be affected by the levels of stress (Bahrami Rad & Rafezi, 2019). Biologically, MS can affect the levels of biological biomarkers such as interleukin-12 (IL12). IL12 is a heterodimer consisting of two subunits, P40 and P35 (Oppmann et al., 2000). Evidence has shown that the levels of interleukin-12 are associated with MS and changes in magnetic resonance imaging (Alexander et al., 2010). Individuals with MS have been shown to have higher levels of interleukin-12 (Losy & Michałowska-Wender, 2002; Van Boxel-Dezaire et al., 2000; Afonina & Beyaert, 2016; Kallaur et al., 2017; Lovett-Racke, & Racke, 2018; Nejatpour, Fathei, & Yaghoubi, 2019).

Psychological interventions such as cognitive-behavioral stress management (CBSM) training may help improve psychological distress such as enduring stress and pain perception, and biological markers such as IL-12. CBSM is a combination of relaxation and cognitive-behavioral techniques and is more common in people with stress-induced physical illnesses. Also, through techniques such as relaxation training, meditation, and biofeedback, this treatment reduces stress and increases effective coping with problems in MS patients (Anagnostouli, Babili, Chrousos, Artemiadis, & Darviri, 2019). Because psychological problems and biological processes in MS can be influenced by stress, CBSM may be effective in reducing the psychological and biological problems of MS. It has been shown that stress and other psychological distress (e.g., depression and anxiety) are important factors in MS patients that their reduction by CBSM may be helpful (Anagnostouli et al., 2019; Asadi Haghighat, Zahrakar, & Farzad, 2019; Ebrahimi & Ghahari, 2020). Therefore, in this study, CBSM was used to evaluate whether it is effective in improving distress tolerance, pain perception, and interleukin-12 in MS patients by reducing or managing stress.

Numerous studies have shown an association between stress or physical stress and psychological distress with interleukin levels (Jones et al., 2018; Felton et al., 2017). Research has also shown that cognitive techniques reduce emotional distress in MS patients (Abolghasemi, Mikaeili, Khoshnoodnia Chomachaei, & Karimi Yousefi, 2018). Also, other studies have reported that CBSM leads to a reduction in depression, stress, and chronic fatigue (Asadi Haghighat et al., 2019; Anagnostol et al., 2019; Taylor, Dorstyn, & Prior, 2020) and a reduction of pain in patients with MS (Asadbeygi, Ahadi, & Mirzaei, 2019; Taub et al., 2017), and also increased distress tolerance in women with breast cancer and men with acquired immunodeficiency syndrome (AIDS) (Habibi, Habibi, Malekzadeh Moghani, & Ghanbari, 2013; Cruess et al., 2000).

Some studies have proven the effectiveness of cognitive-behavioral therapy (CBT) in reducing the inflammatory cytokines such as interleukin-6 in patients with major depressive disorder (Moreira et al., 2015) and inflammatory cytokines in patients with insomnia (Irwin et al., 2015), as well as the positive effect of CBSM to reduce inflammatory cytokines, including interleukin-13 (Lattie, 2015). However, stress management intervention is effective in improving psychological and immune factors, pain (Nazemi, Bahrami Ehsan, Alipour, & Bayat, 2018), and negative emotions (Javanmard & Goli, 2018).

Some studies have shown the effects of CBSM on pain, distress tolerance, and IL-12 in some disorders, but the effects of CBSM on pain, distress tolerance, and IL-12 in MS patients were not evaluated. However, these studies have focused on other aspects or variables of disease except on the variables studied in the present study. Besides, given that stress is an important factor in MS and may

increase distress intolerance, pain, and biomarkers such as interleukins, the present study has focused on CBSM and evaluated the effectiveness of CBSM training on distress tolerance, pain perception, and IL-12 in patients with MS. We hypothesized that CBSM would increase distress tolerance and improve pain perception and IL-12 in patients with MS.

Method

The design of the present study was quasi-experimental with pretest-posttest, follow-up, and control group. The statistical population included all female patients with relapsing-remitting MS who had been referred to Neuroscience and Rehabilitation Research Centers of Tehran Medical Sciences University. Among them, 20 patients were selected through convenience sampling and were randomly assigned to experimental (10 patients) and control groups (10 patients). The experimental group received 8 weekly sessions (60 minutes each session) of the CBSM training based on Antoni, Ironson, and Schneiderman's (2007) therapy, and the control group was placed on the waiting list. This study was performed in the period of winter 2018 to spring 2019. In this study, there was no drop in participants in treatment sessions. To prevent the dropping of participants, they were convinced that treatment sessions could help them reduce the psychological distress and biomarker levels affecting the disease. Training sessions were performed at the Neuroscience and Rehabilitation Research Center of Tehran Medical Sciences University at Sina Hospital by a clinical psychologist under the supervision of the researcher.

The inclusion criteria included a definitive diagnosis of relapsing-remitting MS disease by a neurologist, not receiving psychological treatment during the past 3 months, receiving the same medical therapies, not suffering from mental disorders, not taking psychotropic drugs, lack of other physical illnesses affecting MS, and consciously participating in research. Exclusion criteria were having psychiatric and other physical illnesses, not attending training sessions for more than two sessions, not willing to participate in the research, and receiving psychological therapies for any reason.

CBSM was summarized as follows: Session 1: Introducing the first component of stress management (including awareness of physical responses to stress) and gradual muscle relaxation exercise for 16 muscle groups. Session 2: Teaching the impact of stress on thinking patterns, emotional states, behavior, physical sensations, stress, and how the patient communicates with others. Session 3: Teaching the interrelations of thoughts, emotions, and bodily senses, teaching how to change one's "assessments" in stressful situations, and teaching how to use imagery to relax. Session 4: Introducing common types of negative thinking and cognitive distortions. Session 5: Emphasis on replacing logical thoughts instead of irrational thoughts and learning five steps to replace logical thoughts. Session 6: Learning how to use the techniques learned in life and providing definitions of "coping" and introducing effective and ineffective coping strategies. Session 7: Introducing and teaching steps for an effective coping program. Session 8: Becoming aware of their anger responses and raw patterns, learning better ways to manage anger, and finally completing the posttest.

In this study, the data were analyzed using multivariate analysis of covariance (MANCOVA) and Bonferroni post-hoc test by SPSS-22 software.

Ethical statement

To meet the ethical consideration in this research, participants were asked to participate in research and training sessions with their own desire, and they were told that their information would remain confidential. All participants signed informed consent forms to participate in the study and were trained based on the 1989 revision of the Helsinki

Declaration. This article has been extracted from the doctoral dissertation approved at Payame Noor University, with the ethic code of IR.PNU. REC.1397.006.

Self-report Measures

The Distress Tolerance Scale (DTS): This questionnaire was designed by Simons and Gaher (2005) to assess distress tolerance and contains 15 items and four subscales including tolerance, absorption, appraisal, and regulation, and efforts to alleviate distress. Respondents responded to each item based on a five-point Likert scale, from strongly agree = 1 to completely disagree = 5. Cronbach's alpha coefficient for the total scale and the dimensions of tolerance, absorption, appraisal, and regulation were 0.82, 0.72, 0.82, 0.78, and 0.70, respectively (Simmons & Gaher, 2005). In Iran, Shams et al. (2010) reported that Cronbach's alpha for this questionnaire was 0.67 and its test-retest reliability was 0.79.

The West Haven-Yale Multidimensional Pain Inventory (WHYMPI): This questionnaire was designed by Bernstein, Jaremko, and Hinkley (1995) to evaluate pain perception in three independent parts. The first part contains 20 items related to the subscales of pain intensity, pain interference in daily life, understanding life control, emotional distress and support, and dependence on the spouse or an important person in life. The second part contains 14 items, including three subscales of punitive reactions by others, interest by others, and distress and confusion by others. The last part contains 14 items measuring minor and common activities of the house, outdoor working, and social activities. In Iran, Mirzamani, Safari, Hali Saz and Sadidi (2007) examined the validity of this questionnaire and reported Cronbach's alpha and its test-retest reliability as 0.91 and 0.95, respectively.

Laboratory method

Enzyme-linked immunosorbent assay (ELISA): The ELISA was used to measure IL-12 in experimental and control groups in the pretest, posttest, and follow-up stages. ELISA is a biochemical technique that is mainly used in immunology to identify the presence of an antibody or antigen in a sample. ELISA is based on the binding of antibodies and antigens, which takes place in the substrate of a material with a high binding strength to the protein and plays the role of an absorbent. This process is a 96-cell polyethylene matrix with a 12 x 8 matrix. IL 12 levels were measured

Table 1: Demographic characteristics

Group	Age		Marital status, frequency (%)			Education, frequency (%)			Age of onset of MS		Illness duration	
	Mean	SD	Single	Married	Divorced	Diploma	Under Graduated	Graduated or higher	Mean	SD	Mean	SD
CBSM	31.60	6.74	3 (30%)	7 (70%)	0 (0%)	4(40%)	4 (40%)	2 (20%)	24.30	3.47	7.30	4.83
Control	33.90	6.08	4(40%)	6 (60%)	0 (0%)	4(40%)	6 (60%)	0 (0%)	27.60	5.19	6.30	3.27

based on the blood samples of patients with MS who participated in the present study in the pretest, posttest, and follow-up stages. In this method, the serum was separated from the blood sample by centrifugation and stored in a freezer at -18 C.

Table 2: Mean and standard deviation

		Non-adjusted						Adjusted	
		Pretest		Posttest		Follow-up		Posttest	Follow-up
Variables	**Group**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Distress tolerance	CBSM	36.00	8.93	70.10	2.18	69.90	2.42	68.22	68.20
	Control	29.10	8.24	28.80	8.32	29.15	7.24	30.98	30.80
Pain severity	CBSM	64.90	10.84	40.10	9.80	40.40	9.52	43.13	43.39
	Control	71.20	7.53	71.70	7.26	71.70	7.03	68.67	68.71
Perceived influence of important people	CBSM	41.90	10.46	72.30	7.60	70.90	4.56	72.75	71.95
	Control	42.90	6.84	42.60	6.64	42.60	6.17	42.15	41.55
Doing daily affairs	CBSM	42.90	7.19	69.40	6.85	69.20	6.88	67.65	67.16
	Control	42.30	13.46	43.70	17.09	43.70	16.93	45.45	45.74
Interleukin-12	CBSM	55.61	6.77	36.76	5.98	37.17	5.77	35.42	35.79
	Control	58.52	16.27	58.70	16.23	58.79	16.28	55.84	55.97

Results

Demographic characteristics are presented in Table 1.

The non-adjusted mean and standard deviation of the dependent variables in three stages of pretest, posttest, and follow-up in the experimental and control groups are presented in Table 2. Also, adjusted means after controlling for the pretest are presented in Table 2.

According to Table 2, in the experimental group, the mean of distress tolerance increased in the posttest and follow-up stages compared to the pretest. The mean of pain perception components, including pain intensity, decreased in the posttest and follow-up stages compared to the pretest, and the mean of other components of pain perception, including the perceived influence of important people and doing daily affairs, increased in the posttest and follow-up stages compared to the pretest. Also, in the control group, the mean of these variables in the posttest and follow-up stages did not change compared to the pretest.

Before performing MANCOVA, we assessed the Kolmogorov-Smirnov, M Box, and Levine tests to follow the assumptions. The non-significant results of the Kolmogorov-Smirnov test for the research variables indicated that the data were normally distributed. Also, the non-significant results of the M Box and Levine tests confirmed the assumptions

Table 3: Analysis of covariance to evaluate the effectiveness of CBSM on dependent variables in the two posttest and follow-up stages after controlling for the effect of pretest

Dependent variables	Stage	Sum of squares	df	Mean square	F	Sig	Partial eta squared	Observed power
Distress tolerance	Post-test	5445.02	1	5445.02	482.52	0.001*	0.97	1.00
	Follow-up	5489.96	1	5489.96	470.77	0.001*	0.97	1.00
Pain severity	Posttest	2561.94	1	2561.94	237.24	0.001*	0.95	1.00
	Follow-up	2516.47	1	2516.47	224.65	0.001*	0.95	1.00
Perceived influence of important people	Posttest	3678.08	1	3678.08	228.89	0.001*	0.95	1.00
	Follow-up	3628.29	1	3628.29	240.80	0.001*	0.95	1.00
Doing daily affairs	Posttest	1934.78	1	1934.78	99.18	0.001*	0.88	1.00
	Follow-up	1800.46	1	1800.46	92.16	0.001*	0.88	1.00
Interleukin-12	Posttest	1637.50	1	1637.50	462.80	0.001*	0.97	1.00
	Follow-up	1598.63	1	1598.63	421.67	0.001*	0.97	1.00

* $p<0.001$.

of equality of covariance and homogeneity of variance.

The results of the Wilks' lambda test, as the most common test in multivariate analysis of covariance, indicate that there is a significant difference between the experimental and control groups in posttest ($F = 305.35$, $p< 0.001$) and follow-up ($F = 255.64$, $p< 0.001$) stage. Eta squared also showed that 99% of the variance of the scores of the experimental and control groups were related to group membership in posttest and follow-up.

Table 3 shows the results of the effect of CBSM on distress tolerance, pain perception components, and interleukin-12 in the posttest and follow-up stages after controlling for the pretest. As can be seen, there was a significant difference between the experimental and control groups in the distress tolerance posttest scores ($F= 482.52$, $p< 0.001$), pain perception components, including pain severity ($F = 237.24$, $p< 0.001$), perceived influence of important people ($F = 228.89$, $p< 0.001$), and doing daily affairs ($F = 99.18$, $p< 0.001$), and interleukin-12 ($F = 462.80$, $p< 0.001$). Also, there was a significant difference between the experimental and control groups in the follow-up scores of distress tolerance ($F= 470.77$, $p<0.001$), pain perception component, including pain severity ($F = 224.65$, $p< 0.001$), perceived influence of important people ($F = 240.80$, $p< 0.001$), and doing daily affairs ($F = 92.16$, $p< 0.001$), and interleukin-12 ($F = 421.67$, $p< 0.001$). In other words, despite controlling for the scores of these variables in the pretest, distress tolerance increased in the posttest and follow-up stages. Also, one of the components of pain perception, including pain severity decreased in the posttest and follow-up stages, and its two other components including the perceived influence of important people and doing daily affairs increased in the posttest and follow-up stages. Also, the levels of interleukin-12 decreased in posttest and follow-up. Besides, these changes remained stable in the follow-up stage. Therefore,

Table 4: Pairwise comparison among the pretest, posttest, and follow-up stages for each variable

Variables	Stage comparison		Mean difference	SD	Sig
Distress tolerance	Pretest	Posttest	17.05	4.09	0.002*
		Follow-up	16.95	4.10	0.002*
	Posttest	Follow-up	0.10	0.29	1.00
Pain severity	Pretest	Posttest	12.15	0.73	0.000**
		Follow-up	12.00	0.79	0.000**
	Posttest	Follow-up	0.15	0.17	1.00
Perceived influence of important people	Pretest	Posttest	15.05	3.68	0.002*
		Follow-up	14.35	3.68	0.003*
	Posttest	Follow-up	0.70	1.01	1.00
Doing daily affairs	Pretest	Posttest	13.95	3.25	0.001**
		Follow-up	13.85	3.26	0.001**
	Posttest	Follow-up	0.10	0.39	1.00
Interleukin-12	Pretest	Posttest	10.19	2.43	0.001**
		Follow-up	9.94	2.39	0.002*
	Posttest	Follow-up	0.25	0.15	1.00

* $p<0.01$. ** $p<0.001$.

according to the obtained results, the research hypothesis was confirmed.

We also performed a Bonferroni post-hoc test to pairwise comparison among the pretest, posttest, and follow-up stages for each variable. The results are shown in Table 4. The results showed that there were significant differences between the mean scores of distress tolerance and pain tolerance, pain perception components including pain severity, perceived influence of important people, and doing daily affairs, and interleukin-12 in the posttest and follow-up stages with mean scores of these variables in the pretest. Also, there were no significant differences between posttest and follow-up regarding all variables (Table 4).

Discussion

The aim of the current study was to examine the effectiveness of the CBSM training on distress tolerance, pain perception, and IL-12 in patients with MS. The results showed that CBSM significantly increased patient tolerance, which was stable over time. These results were in line with previous studies (e.g., Habibi et al., 2013; Cruess et al., 2000). Patients with MS have irrational thoughts, such as ‘my illness is unchangeable’, ‘I have no control over the disease’, ‘it is the cause of all my failures in life’, as well as feelings of sadness, depression, and inferiority or anger due to illness, inability to interact with others in the community due to illness, and taking on social and professional roles. In this study, CBSM improved the attitude and interpretation of patients with MS towards life and disease, and also increased distress tolerance in MS patients by educating patients to cope with the inevitable problems of life, to better cope with stressful situations (such as MS) and unpleasant events, as well as to increase resilience (Hassanzadeh, Zare & Alipoor, 2012; Imani, Askarizadeh & Fazilatpour, 2017). CBSM helped patients with MS identify stress-inducing situations, assess negative events differently, and

learn coping strategies to deal with these situations. Thus, patients developed a sense of control by increasing their cognitive-behavioral skills. This sense of control convinced people to take control of uncontrollable situations. Therefore, modifying cognitive assessments, improving coping skills, and teaching how to combine the learned techniques with stressful situations in the life of patients with OCD have led to an increase in their tolerance for emotional distress.

The results of the present study showed that CBSM decreased one of the components of pain perception including pain severity and increased its two other components including the perceived influence of important people and doing daily affairs. Moreover, these changes remained stable over time. These findings were consistent with previous studies (e.g., Montazeri et al., 2016; Taub et al., 2017). Neuro psychologically, the gate control theory of pain believes that it is a kind of gate mechanism in the spinal cord that acts as a mediator in the pain impulses. Opening and closing the gate adjusts the amount of information sent to the brain from the damaged areas. Negative thoughts lead to the opening of the gate, and as a result, more information about the pain passes through it, while positive thoughts close the gate and limit the pain message, so the pain messages can be intensified or reduced (Melzack & Wall, 2016). Therefore, since MS is associated with high levels of stress and emotional distress, and this stress can lead to the opening of pain gate and thus increase patients' pain perception, it can be concluded that the stress management programs can lead to stress management, the closure of the pain gate, and then positive pain perception and subsequent reduction in pain sensation in these patients by focusing on the dysfunctional cognitions and behaviors of MS patients about their illness and replacing cognitions and positive thoughts with them (Mohammadi et al., 2007), on the one hand, and by teaching muscle relaxation, on the other hand.

Before the intervention, patients with MS had ineffective cognitive thoughts about their pain (my pain is incurable and will be with me for the rest of my life, I can't do my daily affairs) and the levels of anger, depression, distress, and negative thoughts (such as this pain or illness is unbearable and deadly and I can't control it) were high, which could increase the pain. This psychological distress leads to increase stress, which in turn reduces the pain verge and worsens the physical condition, and ultimately leads to an increase in the patient's emotional changes (Craig, 2001). During CBSM, patients with MS are taught cognitive techniques (such as identifying negative and irrational thoughts and replacing positive logical thoughts and hopeful mental schemas) and behavioral techniques to control and manage stress (such as training muscle relaxation that activates the parasympathetic system) (Jandaghi, Neshatdoost, Kalantari, and Jabal Ameli, 2012), which changes patient's attitudes (so that my disease can be controlled and I will recover, and pain has no effect on my life and activities), achieves relaxation, and consequently, reduces the negative pain perception and its severity and increase positive attitudes about people influencing them and engaging in daily activities.

The present research revealed that CBSM led to a decrease in IL-12. Besides, these changes remained stable over time. Although no research has been performed on the effectiveness of cognitive-behavioral stress management on biomarkers such as interleukin-12 and this study was the first to examine the effects of this intervention on interleukin-12 in patients with MS, the results of some studies were consistent with our results. For example, Hall (2016) showed that telephone-delivered CBSM could reduce interleukin-6 in people with chronic fatigue syndrome. Moreira et al. (2015) showed that CBSM was able to reduce inflammatory cytokines such as interleukin-6 in patients with major depressive disorder. Lattie

(2015) showed that telephone-delivered CBSM reduced interleukin-13. Berk et al. (2015) showed that cognitive-behavioral therapy was able to reduce stress-related biomarkers such as interleukins-4, -6, and -10 in patients with major depression and chronic medical conditions. Chen et al. (2011) reported that cognitive-behavioral therapy reduced inflammatory cytokines such as interleukin-18 in hemodialysis patients.

Because stress and psychological distress are related to interleukin levels (De Oliveira et al., 2018; Song et al., 2003; Kim et al., 2002), CBSM may reduce interleukin-12 in patients with MS through its effect on reducing stress. Numerous studies have shown an association between stress and physical and psychological stressors with interleukin levels (Brydon et al., 2004; Jones et al., 2018; Marsland et al., 2017; Steptoe, Hamer, & Chida, 2007). Through techniques such as relaxation training, meditation, and biological feedback, CBSM causes nerve relaxation and reduces stress and effective coping with problems (Carlson et al., 2001). Stress, as a multidimensional and multifactorial phenomenon, can be a complication of MS as well as a factor in exacerbating and recurring symptoms of this disease (Jones et al., 2018). CBSM may help improve stress-affected biomarkers by empowering MS patients to cope with the stress caused by this disease, obtaining information about stress resources, and teaching effective coping skills including problem-solving training, teaching muscle relaxation skills, and modifying maladaptive assessments using cognitive reconstruction. CBSM increases people's ability to reduce stress and adapt to stressful situations (Carlson et al., 2001).

Stress management interventions, cognitive-behavioral therapy, or CBSM may be appropriate strategies for positive changes in patients with MS (Reynard, Sullivan, & Rae-Grant, 2014) and reduction of inflammatory cytokines (Antoni et al., 2009; Erwin et al., 2015). Research has shown that stress-based therapies, such as cognitive-behavioral stress management training and mindfulness-based stress reduction, have improved biological indicators such as reducing interleukin-6 in people with major hypertension (Sheibani, 2018). Considering that immune system dysfunction is one of the most important factors in the etiology of diseases, it has recently been stated that stress has an adverse effect on the course of diseases and exacerbates the disease activity by intensifying cognitive immune dysfunction and effect on the cytokine network (Levenstein et al., 2000; Mawdsley & Rampton, 2005). In the CBSM training, participants are taught relaxation techniques. Learning relaxation techniques allows people to recognize the physical symptoms of stress and learn how to control the physical symptoms of stress by mastering relaxation and using these techniques (Shokouhiyekta & Parand, 2012). Because the body's physiological responses to stress can occur over a wide range of physical symptoms, training relaxation techniques can reduce the levels of stress hormones (including cortisol) and physiological symptoms of stress by increasing diaphragmatic breathing and reducing stress experience (Chandola, Heraclides, & Kumari, 2010), and consequently affect the level of biomarkers.

This study has some limitations: 1- This study was performed only on women with MS and may not be generalizable to the male population with this disease. 2- This study was performed on patients with relapsing-remitting MS and cannot be generalized to other types of this disease such as primary-progressive MS, secondary-progressive MS, and progressive relapsing MS. 3- The findings of this study have been obtained using self-report tools and these tools may lead to bias in participants' responses. Despite these limitations, the present study showed that CBSM training is effective in increasing anxiety tolerance, improving pain perception, and reducing inflammatory biomarkers such as interleukin-12 in women with

MS. According to these results, the use of this psychological treatment can be used by therapists in medical centers as well as in MS associations.

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