



COMPARISON EFFECTIVENESS OF MBSR AND CBT ON INTERLEUKIN 6 AND OXIDATIVE STRESS IN HYPERTENSIVE PATIENTS

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ABSTRACT

Cardiovascular diseases are the leading cause of death in developing countries. Research has shown that the level of oxidative stress and interleukin 6 (IL-6) is higher in individuals with hypertension than individuals with normal blood pressure. Therefore, the aim of the present randomized clinical trial study was to compare the effectiveness of mindfulness-based stress reduction (MBSR) and cognitive-behavioral therapy (CBT) on oxidative stress and interleukin 6. Sixty patients with primary hypertension were divided into two intervention groups (MBSR and CBT) and one control group. Oxidative stress and IL-6 were measured by prooxidant-antioxidant balance (PAB) and ELISA method (Biovendor kit), respectively. Data analysis was carried out using ANOVA and MANCOVA in SPSS Ver.19. The results showed that MBSR significantly reduced oxidative stress. Also, MBSR and CBT significantly reduced IL-6 levels.

KEYWORDS: *Hypertension; Interleukin 6; Oxidative Stress; Mindfulness-Based Stress Reduction; Cognitive- Behavioral Stress Management*



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INTRODUCTION

Cardiovascular diseases are the leading cause of death in developing countries to the extent that they account for 1 out of 8 deaths worldwide. Therefore, hypertension is the third leading cause of death in the world¹. According to Global Burden of Disease Study, hypertension was identified as one of the three major risk factors for global burden of disease². Chronic non-communicable diseases, especially cardiovascular diseases also account for a large part of the causes of death and disability in Iran. Cardiovascular diseases, the first cause of death, also account for 39.3% of all deaths in the country³⁻⁴. Therefore, it is necessary to identify major risk factors and design effective therapies. The overall hypertension is related to emotional states or environmental conditions. Various studies have shown the impact of various psychological factors such as anxiety and stress on the development and spread of cardiovascular diseases, including hypertension. Physiological mechanisms for blood pressure regulation may be affected by stress. Chronic stress leads to increased oxidative stress (OxS) and IL-6 processes⁵. Oxidative stress is a biochemical process that increases the risk of chronic diseases⁶. Free radicals and, especially, reactive oxygen species (ROS) are the most important factors leading to the formation of oxidative stress reactions. Oxygen is the most important free radical in humans. The oxygen molecule exposed to various radiations, stress, tobacco smoke and etc. destroys other molecules, cells and DNA by taking one electron from other molecules. These free radicals lead to a variety of cancers, diabetes, heart disease, brain damages, muscular problems, early aging, eye injuries, and, in general, weakness of the immune system. In the meantime, antioxidants are considered as the main means of combating free radicals and regenerating damaged cells since they degenerate these free radicals and promote the immune system's performance against a variety of diseases. There are certain systems to cope with the damage caused by free radicals in the body that are called "antioxidant defense system. Normally, there is a balance between the production of free radicals and this system in a healthy person, but if this balance is disrupted for any reason, the results state is called oxidative stress, which can be involved in the pathogenesis of more than 100 different types of diseases through multiple mechanisms, including metabolic degradation and impaired intracellular calcium homeostasis⁷⁻⁹. Although a higher ratio of

low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) is considered as an indicator of the diagnosis of cardiovascular diseases, the findings suggest that some individuals with cardiovascular diseases have had normal LDL-C and HDL-C. According to previous researches, inflammatory factors are involved in the spread of cardiovascular diseases¹⁰. Thus, researchers have shifted their attention to inflammatory indices such as: fibrinogen, haptoglobin, interleukin 6, and C-reactive protein as independent predictors of the cardiovascular diseases in the past decade¹¹. Therefore, the aim of the present study was to evaluate the effectiveness of treatment of MBR and CBT on oxidative stress and IL-6 in patients with essential hypertension. The aim of mindfulness-based interventions is to reduce psychological symptoms of distress and promote the quality of life, both in terms of mental and physical health status. The aim of these interventions is to create a clear and non-judgmental mindfulness of what is happening at the moment. Many clinical trials have shown the effectiveness of mindfulness exercises in reducing stress and disturbance in clinical and non-clinical populations¹²⁻¹³. Another approach used to manage hypertension is the cognitive behavioral approaches for stress management, which uses various types of relaxation, cognitive restructuring, coping strategies training, anger management and self-assertion. The aim of this research was to investigate the effectiveness of MBSR and CBT on oxidative stress and IL-6 in patients with essential hypertension.

MATERIALS AND METHODS

This research was a randomized clinical trial study with pretest-posttest control group and approved with registration code of IRCT2017103137145N1. The statistical population of this research included all patients with cardiovascular diseases referring to health centers and hospitals of Iran University of Medical Sciences (Department of Cardiology, Rasoul-Akram Hospital, Niayesh St, Sattarkhan Ave, Tehran, Iran). Of these, 60 patients who met the inclusion and exclusion criteria were selected using convenience sampling and randomly divided into two intervention groups (MBSR and CBT) and one control group (N=20 in each group) (taking into account the drop-out rate of 5 individuals). Sample size and adequacy were obtained based on the main statistical methods and previous studies. The inclusion criteria included identification of

essential hypertension according to a cardiologist's diagnosis and this hypertension was not controlled despite drug therapy, the education level of at least middle school (8th grades), individuals aged 30-60 years, those who have given their willingness to participate in the research based on a signed informed written form. The Institutional ethical committee certificate was issued with IR.IJMS.FMD.REC1396.9211521215 code in this research. Exclusion criteria included secondary hypertension, major depressive disorder, generalized anxiety disorder, panic disorder and post-traumatic stress disorder during the past year, and receiving MBSR and CBT therapy by a psychologist or psychiatrist in the past. After being selected, a number was assigned to each patient and then randomly entered into one of these three groups by drawing. The remaining blood sample (which was taken from patients to perform diagnosis and periodical evaluation) of patients who had blood tests during the month before the intervention, was used to assess biological variables of the research before the intervention. Also, the remaining blood sample (which was taken from patients to perform diagnosis and periodical evaluation) of patients who had blood tests during the month after the intervention, was used to assess biological variables of the research after the intervention. The remaining blood sample of patients was used to carry out the sampling in order to evaluate the biochemical variables. Samples were divided into 0.5 cc microtubes and stored in a freezer at 70°C until biochemical tests were performed. Liquid nitrogen flasks were used to transfer samples to the laboratory. Three replications were performed to increase the accuracy of tests. Finally, the average of three replications was entered into the statistical analysis as the final result. Oxidative stress was measured by prooxidant-antioxidant balance (PAB). This evaluation method has been used in valid researches¹⁴⁻²⁰. Serum IL-6 levels were measured by ELISA using IL-6 kit (Biovendor, Germany). A group of patients, along with drug therapies, received 8 sessions of MBSR group intervention on a weekly basis. Each session lasted for 1.5 hours. The MBSR treatment was performed in accordance with the 8th session protocol of Jon Kabat-Zinn (1992). The other group, along with drug therapy, received 8 sessions of CBT group intervention based on the 8th session protocol of Anthony, Ironson and Schneiderman (2007). Each session lasted for 1.5 hours. The control group received only the treatment as usual (TAU), which was a

drug therapy. Data analysis was carried out using multivariate analysis of covariance (MANCOVA) and ANOVA in SPSS software (Version 19). CBT sessions were structured according to the cognitive-behavioral stress management book. The structure of the sessions was as follows:

Session 1: Introduction of stressors and stress responses, gradual muscle relaxation for 16 muscle groups, blood pressure measurement.

Session 2: Stress effects, stress symptoms, gradual muscle relaxation for 8 muscle groups.

Session 3: Diaphragmatic breathing, gradual muscle relaxation for the four muscle groups, visualization and relaxation, communication of thoughts and excitements, thought power practicing.

Session 4: Diaphragmatic breathing along visualization, gradual passive muscle relaxation, together visualization of a specific location, negative thinking and cognitive distortions, negative thoughts and behaviors, training on how to identify negative thoughts.

Session 5: Integration of relaxation, introducing self-taught training and self-taught exercise for heaviness and heat, the difference between rational and irrational self-talk, practices the replacement of rational thoughts.

Session 6: Self-taught training for heart rate, breathing, abdomen and forehead, defining coping, and a variety of effective and ineffective coping strategies.

Session 7: The logic of self-taught training with visualization and self-induction, effective coping steps, effective coping practice, anger management training.

Session 8: Courage training, problem-solving training, personal stress management.

The MBSR-based group intervention was conducted on the basis of the 8th session approach developed by Jon Kabat Zinn. The content of the MBSR 8 sessions was as follows:

Session 1: Communication skills and conceptualization, the need to use mindfulness training, providing explanations about the auto-guidance system.

Session 2: Review of last week's homework, body scan, meditation exercises, mindfulness-based breath training (MBRT).

Session 3: Review of last week's homework, sitting meditation, practice review, three-minute breathing space training.

Session 4: Review of last week's homework, a five-minute practice of "seeing or hearing," mindfulness-based breath training and body scan.

Session 5: Review of last week's homework, breathing exercises, sitting meditation (awareness of breathing, body, sounds, and thoughts), explanations about stress and its relationship to blood pressure, awareness of the effect of pleasant and unpleasant events on feelings, thoughts and body feelings.

Session 6: Review of last week's homework, vigilant yoga, discussion of different views of thoughts or substitute thoughts, sitting meditation (Mindfulness of sounds and thoughts).

Session 7: Review of last week's homework, sleep hygiene, repeating the homework of the previous sessions, and providing a list of fun activities.

Session 8: Review of last week's homework, body scan, summing up the sessions, Check out and discuss about the programs and continuing the exercises.

RESULTS AND DISCUSSION

As shown in the table 1, there is a significant difference in oxidative stress between mindfulness-based stress reduction group and control group (0.549). There is no significant difference between cognitive-behavioral group and control group. Additionally, there was no significant difference between cognitive-behavioral group and mindfulness group in terms of the oxidative stress. As shown in the table 2 there is a significant difference between the studied groups in terms of the IL-6 variable. In addition, the effect size of 0.548 also indicates that approximately 55% of the variable of IL-6 variance is explained by the grouping variable (i.e., type of treatment). The lower level of IL-6 scores of the MBSR group in the post-test (28.042) compared with the cognitive-behavioral group (CBT) (32.425) indicates the higher effectiveness of MBSR group.

Table 1
Analysis of Variance (ANOVA) for oxidative stress

	CBT (n = 15)		MBSR (n = 16)		Control (n = 15)		F	P	Pairwise Comparisons			
	M (SD)		M (SD)		M (SD)							
	Pre	Post	Pre	Post	Pre	Post						
oxidative stress	1.71 (.54)	1.29 (.07)	1.58 (.45)	1.06 (.07)	1.46 (0.48)	1.61 (.07)	5.49	= .008	CBT < Control MBSR < Control MBSR < CBT			

Table 2
Analysis of Covariance (ANCOVA) for Interleukin 6 by group at pre-test and post-test

	CBT (n = 15)		MBSR (n = 16)		Control (n = 15)		F	P	ES	Pairwise Comparisons				
	M (SD)		M (SD)		M (SD)									
	Pre	Post	Pre	Post	Pre	Post								
Interleukin 6	38.37 (6.89)	32.42 (.93)	41.44 (13.13)	28.04 (.92)	33.13 (10.36)	37.79 (.96)	25.48	< .001	.548	CBT < Control MBSR < Control MBSR < CBT				

The results of Aghayousefi et al.'s study showed that there is a positive significant correlation between the methods of coping with excitement-oriented stress with the cognitive biomarker of IL-6 and a negative significant correlation between methods of coping with problem-oriented stress with IL-6²¹. Tomfohr stated that there was a significant and inverse relationship between trait

mindfulness with hypertension and IL- 6 levels²². Rosado-Pérez et al. showed that Tai Chi (a type of meditation) further reduces the oxidative stress (OxS) process as compared to walking, which are statistically significant²³. Many research findings show that the pathophysiology of the chronic stress can lead to increased oxidative stress activity (OxS), which is in turn associated with heart

diseases, rheumatoid arthritis, hypertension, Alzheimer's disease, Parkinson's disease and atherosclerosis and ultimately aging²⁴⁻²⁶. The results of González et al.'s study indicated that there was a direct and significant correlation between increased IL-6 level and hypertension²⁷. The results show that anti-inflammatory treatments reduce the incidence of acute coronary syndrome by reducing the level of this agent²⁸. In a research on 114 male subjects, Qureshi et al. showed that stress plays a role in increasing plasma IL-6 levels. They also found that there is a significant correlation between IL-6 levels and systolic and diastolic blood pressure²⁹. The results of this study were consistent with the aforementioned researches.

CONCLUSION

Stress can exacerbate the disease through affecting various body systems, especially the cardiovascular system or autoimmune system. Stress leads to an increase in LDL, HDL, and triglyceride levels. Changes in plasma lipid levels are a response to acute psychological stress, which increases the risk of cardiovascular diseases and hypertension. Chronic stress is associated with increasing arterial pressure and impaired autonomic regulation of cardiovascular function. Increasing the activity of the sympathetic nervous system (SNS) along with

the suppression of the vagus nerve and reducing the sensitivity of the baroreceptors can provide a therapeutic mechanism in case of the psychological factors and the incidence of hypertension. The limitation of this study is the lack of a follow-up. Therefore, it is recommended to use follow-up tests in future studies to measure durability of effects of these treatments.

AUTHOR CONTRIBUTION STATEMENTS

Behrooz Birashk conceived of the presented idea. Farshad Sheybani developed the theory and performed the computations. Banafsheh Gharraee verified the analytical methods. Farshad Sheybani carried out the experiment. Mohamadreza Pirmoradi helped supervise the project. Shokoufeh Hajssadeghi designed the study.

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CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol.* 2014;11(5):276-89. Available from: <http://dx.doi.org/10.1038/nrcardio.2014.26>
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2224-60.
3. Abdollahy AA, Bazrafshan HR, Salehi A, Behnampour N, Hosayni SA, et al. Epidemiology of hypertension among urban population in Golestan province in north of Iran. *J Gorgan Univ Med Sci.* 2007;8(4):37-41.
4. Janghorbani M, Amini M, Gouya MM, Delavari A, Alikhani S MA. Nationwide survey of prevalence and risk factors of prehypertension and hypertension in Iranian adults. *J Hypertens.* 2008;26(3):419-26.
5. Epel E. Psychological and metabolic stress: A recipe for accelerated cellular aging? *Hormones.* 2009;8(1):7-22. Available from: <http://dx.doi.org/10.14310/horm.2002.1217>
6. Mendoza-Núñez VM, Ruiz-Ramos M, Sánchez-Rodríguez MA, Retana-Ugalde R, Muñoz-Sánchez JL. Aging-Related Oxidative Stress in Healthy Humans. *Tohoku J Exp Med.* 2007;213(3):261-8. Available from: <http://dx.doi.org/10.1620/tjem.213.261>
7. Cherubini A, Ruggiero C, Polidori MC, Mecocci P. Potential markers of oxidative stress in stroke. *Free Radic Biol Med.* 2005;39(7):841-52. Available from: <http://dx.doi.org/10.1016/j.freeradbiomed.2005.06.025>
8. Malekiran A, Rahzani K, Ranjbar A, Shariatzadeh M BH. Estimation of total antioxidant oxidant capacity of saliva in

Arakstudents 15-17 years. *J Shahrekord Univ Med Sci.* 2006;8(2):67-71.

9. Palizvan M, KHADEMI S, Ghazavi A MG. Correlation of two way active avoidance learning with Nitric Oxide and Ferric reduction/antioxidant power in rats. *J Arak Uni Med Sci.* 2006;9(4):1-8.

10. Blake GJ, Ridker PM. Inflammatory biomarkers and cardiovascular risk prediction. *J Intern Med.* 2002;252(4):283-94. Available from: <http://dx.doi.org/10.1046/j.1365-2796.2002.01019.x>

11. DONGES CE, DUFFIELD ROB, DRINKWATER EJ. Effects of Resistance or Aerobic Exercise Training on Interleukin-6, C-Reactive Protein, and Body Composition. *Med Sci Sport Exerc.* 2010;42(2):304-13. Available from: <http://dx.doi.org/10.1249/mss.0b013e3181b117ca>

12. Fjorback LO, Arendt M, Ørnboel E, Fink P, Walach H. Mindfulness-Based Stress Reduction and Mindfulness-Based Cognitive Therapy - a systematic review of randomized controlled trials. *Acta Psychiatr Scand.* 2011;124(2):102-19. Available from: <http://dx.doi.org/10.1111/j.1600-0447.2011.01704.x>

13. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* 2010;78(2):169-83. Available from: <http://dx.doi.org/10.1037/a0018555>

14. Antunovic T, Stefanovic A, Gligorovic Barhanovic N, Miljkovic M, Radunovic D, Ivanisevic J, et al. Prooxidant-antioxidant balance, hsTnI and hsCRP: mortality prediction in haemodialysis patients, two-year follow-up. *Ren Fail.* 2017;39(1):491-9. Available from: <http://dx.doi.org/10.1080/0886022x.2017.1323645>

15. Roh H-T, So W-Y. The effects of aerobic exercise training on oxidant-antioxidant balance, neurotrophic factor levels, and blood-brain barrier function in obese and non-obese men. *J Sport Heal Sci.* 2017;6(4):447-53. Available from: <http://dx.doi.org/10.1016/j.jshs.2016.07.006>

16. Rahsepar AA, Pourghadamayari H, Moohebati M, Parizadeh SMR, Tavallaie S, Paydar R, et al. Prooxidant-anti-oxidant balance is not associated with extent of coronary artery disease. *Clin Biochem.* 2011;44(16):1304-8. Available from: <http://dx.doi.org/10.1016/j.clinbiochem.2011.08.1133>

17. Rahsepar AA, Mirzaee A, Moodi F, Moohebati M, Tavallaie S, Eshraghi A, et al. Anti-Heat Shock Protein 27 Titers and Oxidative Stress Levels are Elevated in Patients With Valvular Heart Disease. *Angiology.* 2012;63(8):609-16. Available from: <http://dx.doi.org/10.1177/0003319711433308>

18. Sahebkar A, Pourghadamayari H, Moohebati M, Parizadeh SMR, Falsoleiman H, Dehghani M, et al. A cross-sectional study of the association between heat shock protein 27 antibody titers, pro-oxidant-antioxidant balance and metabolic syndrome in patients with angiographically-defined coronary artery disease. *Clin Biochem.* 2011;44(17-18):1390-5. Available from: <http://dx.doi.org/10.1016/j.clinbiochem.2011.09.011>

19. Rahsepar AA, Mirzaee A, Moodi F, Moohebati M, Tavallaie S, Eshraghi A, et al. Prooxidant-Antioxidant Balance and Antioxidized LDL Antibody Level Values and Cardiac Function in Patients with Coronary Artery Disease. *Cardiology.* 2012;122(4):203-9. Available from: <http://dx.doi.org/10.1159/000339273>

20. Ghayour-Mobarhan M, Pourghadamayari H, Rahsepar Ali A, Tavallaie S, Parizadeh SMR, Moohebati M, et al. Oxidative levels and its relation with extent and severity of coronary artery disease. *Clin Biochem.* 2011;44(13):S156. Available from: <http://dx.doi.org/10.1016/j.clinbiochem.2011.08.389>

21. Aghayousefi A, Alipoor A, Shaghaghi F SN. Relationship between coping ways with stress and IL-6 Immunologic biomarker in Coronary Heart Disease Patients. *Bimon J Hormozgan Univ Med Sci.* 2013;17(2):155-65.

22. Tomfohr LM, Pung MA, Mills PJ, Edwards K. Trait mindfulness is associated with blood pressure and interleukin-6: exploring interactions among subscales of the Five Facet Mindfulness Questionnaire to better understand relationships between mindfulness and health. *J Behav Med.* 2014;38(1):28-38. Available from:

http://dx.doi.org/10.1007/s10865-014-9575-4

23. Rosado-Pérez J, Ortiz R, Santiago-Osorio E, Mendoza-Núñez VM. Effect of Tai Chi versus Walking on Oxidative Stress in Mexican Older Adults. *Oxid Med Cell Longev.* 2013;2013:1–8. Available from: <http://dx.doi.org/10.1155/2013/298590>

24. Filippin LI, Vercelino R, Marroni NP, Xavier RM. Redox signalling and the inflammatory response in rheumatoid arthritis. *Clin Exp Immunol.* 2008;152(3):415–22. Available from: <http://dx.doi.org/10.1111/j.1365-2249.2008.03634.x>

25. Kumar KV, Das UN. Are Free Radicals Involved in the Pathobiology of Human Essential Hypertension? *Free Radic Res Commun.* 1993;19(1):59–66. Available from: <http://dx.doi.org/10.3109/10715769309056499>

26. Ong SLH, Zhang Y, Whitworth JA. REACTIVE OXYGEN SPECIES AND GLUCOCORTICOID-INDUCED HYPERTENSION. *Clin Exp Pharmacol Physiol.* 2008;35(4):477–82. Available from: <http://dx.doi.org/10.1111/j.1440-1681.2008.04900.x>

27. González GE, Rhaleb N-E, D'Ambrosio MA, Nakagawa P, Liu Y, Leung P, et al. Deletion of interleukin-6 prevents cardiac inflammation, fibrosis and dysfunction without affecting blood pressure in angiotensin II-high salt-induced hypertension. *J Hypertens.* 2015;33(1):144–52. Available from: <http://dx.doi.org/10.1097/jjh.0000000000000358>

28. Ikeda U, Ito T, Shimada K. Interleukin-6 and acute coronary syndrome. *Clin Cardiol.* 2001;24(11):701–4. Available from: <http://dx.doi.org/10.1002/clc.4960241103>

29. Qureshi GM, Seehar GM, Soomro AM, Pirzado ZA AS. Association of blood IL-6, Cortisol and Haemodynamics in Healthy adults with stress: A possible role in early atherogenesis. *Sindh Univ Res Journal-SURJ (Science Ser.* 2009;41(2).