

ORIGINAL ARTICLE

Effects of BFR training in serum NRG-1 and IL-6 in overweight postmenopausal women

Zeinab Rezaee¹, Seyed Ali Akbar Hashemi Javaheri¹, Amir Rashidlamir¹, Onur Oral², Evangelia Stavropoulos³

¹Faculty of Sport Sciences, Ferdowsi University of Mashhad, Mashhad, Iran, ²Ege University, Faculty of Sports Sciences, Izmir, Turkey, ³Master of Research in Information and Communication, University of Lorraine, France

ABSTRACT

Introduction: Menopause is a noticeable period in women's life accompanied by some physiological and psychological changes leading to health conditions such as obesity, overweighting, cardiovascular, and other inflammatory diseases.

Aim: Due to the importance of health cares in this period and the effectiveness of exercise training to attenuate the symptoms, we aimed to compare the effects of an emerging exercise tool by blood flow restriction in limbs on two public health-related cytokines, IL-6 (Interleukin-6) and NRG-1 (Neuregulin-1) in comparison with traditional training in overweight postmenopausal women.

Materials-Methods: 30 overweight post-menopausal women were randomly assigned into BFR (Blood Flow Restriction), HI (High Intensity), LI (Low Intensity) groups (n=10) and performed eight weeks of concurrent training three days a week. Two lower body and two upper body exercises at 20%1RM (20% of one repetition Maximum) load for BFR and LI groups and at 80%1RM (80% of one repetition Maximum) load for HI group in addition to 20 minutes of aerobic training at the end. IL-6 and NRG-1 levels were measured before and after the eight weeks of training sessions.

Results: Group differences in IL-6 levels were observed in BFR and HI groups ($p=0.001$ in both groups) but not in LI group ($p=0.29$). Differences between groups were significant between BFR and LI ($p=0.00$) and HI and LI ($p=0.007$) but not between BFR and HI ($p=0.11$). For NRG-1 levels, group differences were observed in all three groups ($p=0.001$), ($p=0.003$), ($p=0.007$) and the differences between groups for NRG-1 levels were significant between BFR and LI ($p=0.001$) and HI and LI ($p=0.038$) but not between BFR and HI ($p=0.065$).

Conclusion: Low-intensity BFR training and high-intensity traditional resistance training are functioning similarly on the levels of IL-6 and NRG-1 in postmenopausal women and low-intensity training with BFR is more effective than low-intensity traditional training in this proposition.

Keywords: BFR training, Nerogulin-1, NRG-1, Interleukin-6, IL-6, post-menopausal women, Menopause

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INTRODUCTION

Menopause is a considerable period in women's life comprising some fundamental physiological and psychological changes that may lead to losing some health parameters [1,2]. Menopausal women are exposed to some diseases such as cardiovascular diseases, osteoporosis, urogenital atrophy, sexual problems, hot flushes, psychiatric symptoms, sleep disorders, and metabolic syndrome [2-5].

This period is defined by menses cease, which is related to endocrine changes and the β -estradiol deficiency [2,5] that can affect the quality and quantity of postmenopausal women's life³. Overweighing, obesity, and sarcopenia are the outstanding components of metabolic syndrome after the onset of the menopause period [6,7]. Since menopause is accompanied by hormonal changes and consequently increasing adipose tissue and decreasing muscle mass, many molecular changes are observed during this period in different tissues including cytokine alternations [8].

Among these intracellular messengers, Interleukin-6 (IL-6) and Neuregulin-1 (NRG-1) can be respectively the representatives of inflammatory status and degenerative conditions in tissues, especially in cardiovascular health assessments [9-11].

Large pieces of evidence reveal that IL-6, a pro-inflammatory cytokine, increases in menopause that can negatively affect cardiovascular health and body composition [12,13] (Bakker & Jaspers, 2015; Pfeilschifter et al., 2002), and conversely, NRG-1, a cardioactive

growth factor is influential in cardiac cells development and maintenance [10, 14].

It is widely expressed that regular exercise can be a beneficial strategy to manage menopausal symptoms [15-17] and attenuate these ailments conditions by anti-inflammatory and anti-oxidative effects [16]. Moreover, recent studies have shown that resistance training with blood flow restriction can be practical to increase muscle mass and strength improving body composition in older adults including post-menopausal women [18-21]. We aimed to study the effects of BFR training, as an emerging training tool, on serum levels of IL-6 and NRG-1 as indicators of the health condition in menopausal women and compare it with traditional resistance routines.

METHODS

Ethical considerations

All the stages of this experimentation were conducted following the ethical standards adopted by the Ferdowsi University of Mashhad Research Ethics Committee and in compliance with international ethical guidelines.

Subjects

A total of 30 overweight postmenopausal women (Table 1) voluntarily participated in this research project following the inclusion criteria: aged more than 50, being in menopause period, non-smoker, and non-alcohol drinker, overweight, and inactive for at least six months,

Variable Groups	BFR (n=10)	HI (n=10)	LI (n=10)
Age (y)	61.83	54.2	58.2
BMI (kg/m ²)	28.8	28.58	28.4
BFP (%)	36.01	38.02	37.54

Table 1. The basic characteristics of the participants.

Abbreviations: BMI (Body Mass Index), BFP (Body Fat Percentage), BFR (Blood Flow Restriction), HI (High Intensity), LI (Low Intensity), 80%1RM (80% of one repetition Maximum), 20%1RM (20% of one-repetition maximum)

and randomly divided into three concurrent training (Resistance + Aerobic) groups. All participants were informed about the whole project and signed a consent form.

Training protocol

The BFR group performed the resistance training using BFR cuffs with 20%1RM load, the HI group performed the resistance training with 80%1RM load, and the LI group performed with 20%1RM load.

All three groups' start of training was a 10-minute walking on a treadmill as a warm-up and then performed a resistance training routine according to the protocol (Table 2) followed by a 20-minute walking on a treadmill with a 45% HR peak as the aerobic training and performed the routine three days a week for eight weeks.

In every session, after warm-up, all three groups' participants performed three sets of leg press machines, leg extension machines, biceps curl, and triceps extension machines with the specified loads for each group.

BFR intervention

Blood flow restriction cuffs were applied for blood occlusion in proximal sites of legs and arms with 5 cm width for arms and 10 cm for legs.

The external pressure of the arm cuffs was 70 mmHg in the first two weeks and then exceeded 100 mmHg, and for the leg cuffs, it was 70 mmHg in the first two weeks and was promoted to 120 mmHg by the end of the project.

The cuffs remained unflared during the three sets of a movement and then flared for three minutes rest between movements.

Movement	Time or Sets	BFR group Intensity/Reps	HI group Intensity/Reps	LI group Intensity/Reps
Warm-up (walking on the treadmill)	10 min			
Leg press machine	3 sets	20% 1RM 15 reps.	80% 1RM 12 reps.	20% 1RM 15 reps.
Leg extension machine	3 sets	20% 1RM 15 reps.	80% 1RM 12 reps.	20% 1RM 15 reps.
Biceps curl machine	3 sets	20% 1RM 15 reps.	80% 1RM 12 reps.	20% 1RM 15 reps.
Triceps extension machine	3 sets	20% 1RM 15 reps.	80% 1RM 12 reps.	20% 1RM 15 reps.
Aerobic training (walking on the treadmill)	20 min	45% HR peak	45% HR peak	45% HR peak
Cooldown (stretches)	5 min			

Table 2. The resistance training program.

Assessments

The first blood samples were taken one day before the training sessions beginning at 8 AM while the participants had undergone 10 hours of fasting, and the second sampling was done 48 hours after the last training session under the same conditions as the first time.

The serum samples were kept in a -80°C freezer and then analyzed with IL-6 and NRG-1 ELIZA kits (Eastbiopharm, China).

The anthropometric measurements, including height and weight, were assessed for calculating BMI, and a body composition analyzer (Inbody 770) was used to determine BFP%.

Statistical analysis

After the results were obtained, descriptive statistics were used to determine the means and standard deviations. The Shapiro-Wilk test was then used to check the normality

Variables	Groups	Analyze Time		P-value within the groups	P values between the groups
		Pre-test	Post-test		
IL-6	BFR	11.16±1.59	9.53±1.20	0.001	0.001
	HI	13.52±2.16	12.34±2.42	0.001	
	LI	12.86±2.08	12.50±2.24	0.29	
NRG-1	BFR	14.19±3.89	19.38±3.43	0.001	0.001
	HI	14.90±1.36	18.17±2.07	0.002	
	LI	13.93±1.69	14.84±1.86	0.007	

Table 3. Amount of the biochemical variables in pre-and post-analyses.

of the data. To examine the significance of differences between means, one-way ANOVA was used and the paired-sample T-test was used to analyze the differences in means within the groups. Differences in means between each pair of groups were assessed using Tukey's posthoc test. Data analysis was done using SPSS software version 22, while figures were plotted with Excel software. Statistical significance was considered at the level of $p < 0.05$.

RESULTS

The results showed a significant difference in the BFR and the HI groups in baseline and post-training levels of IL-6 ($P=0.00$), but no significant difference was observed in the LI group ($p=0.29$) (Table 3). The significance of differences between means of IL-6 levels by one-way ANOVA was observed ($p=0.001$).

The Tukey's posthoc test showed the difference between the BFR and the HI groups in IL-6 levels was not significant ($p=0.11$), but it was significantly different between BFR and LI groups ($p=0.00$), between the HI and the LI groups, there was also a significant difference ($p=0.007$) (Table 4, Figure 1).

Variables	Groups	P-value between the groups
IL-6	BFR-HI	0.11
	BFR-LI	0.001
	HI-LI	0.007
NRG-1	BFR-HI	0.065
	BFR-LI	0.001
	HI-LI	0.038

Table 4. The results of Tukey's test.

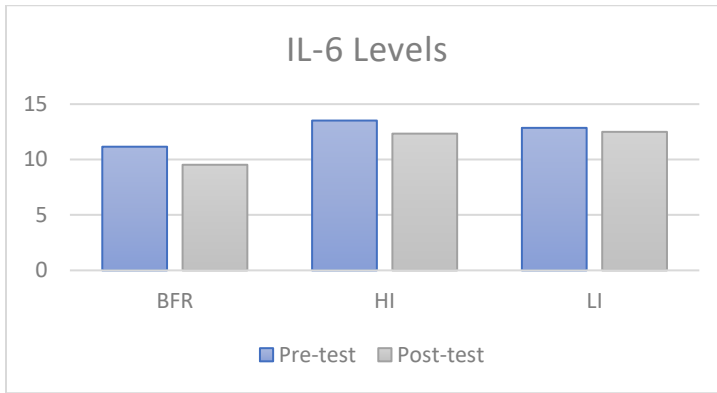


Figure 1. Pre- and post-training levels of IL-6 in three groups.

Regarding the NRG-1 levels, significant differences were observed in all three groups ($p=0.001$), ($p=0.003$), ($p=0.007$) in pre-and post-training levels (Figure 2), and the significance of differences between means of NRG-1 levels by one-way ANOVA was observed too ($p=0.001$).

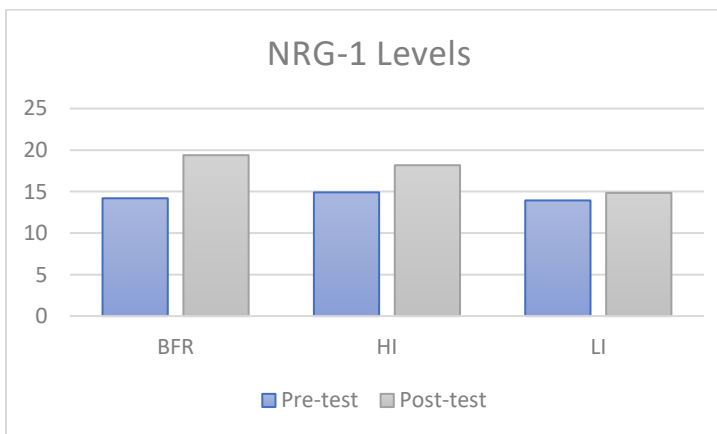


Figure 2. Pre-and post-training levels of NRG-1 in three groups.

When comparing differences between groups, no significant difference was observed between the BFR and the HI groups ($p=0,065$), but differences between the BFR and the LI

group ($p=0.00$) and between the HI and the LI groups ($p=0.038$) were significant.

DISCUSSION

The present study aimed to observe the effects of BFR training on serum levels of IL-6 and NRG-1 after eight weeks of training and to compare it with high and low traditional resistance training in overweight postmenopausal women.

According to our results, serum levels of IL-6 decreased, and conversely, NRG-1 levels increased after eight weeks of training, and the most changes were observed in the BFR group compared with the HI and LI groups.

Blood flow restriction training, also called KAATSU training, was introduced to the athletic and rehabilitation world in the last decades of the 20th century by venous blood occlusion in proximal portions of limbs that are effective on muscle hypertrophy and strength gain in different populations [22-24]. The present evidence shows that this new training method is not only influential on muscle size and strength but also is effective on cardiovascular and endocrine systems [18,19,25,26] and may be beneficial for increasing aerobic capacity due to the elevating heart rate and more muscle fibers recruitments while exercising with BFR cuffs [27].

Since the beginning of BFR training, many studies have been performed in older populations, including postmenopausal women, suggesting that exercising with BFR cuffs could be an effective alternative to the

traditional high-intensity training that has too much pressure on joints [18,19,28].

Menopause is associated with increased inflammation and pro-inflammatory cytokines, including IL-6, due to the decline in estrogen levels [29]. Interleukin-6 (IL-6), detected in 1986 as a B-cell differentiation factor, today is known as a multi-functional cytokine associated with immune and acute phase responses and plays a significant role in the pathogenesis of some autoimmune diseases [30]. Overproduction of IL-6 implicates a variety of chronic inflammatory diseases such as obesity, type 2 diabetes, atherosclerosis, and menopause [31,32] which are reduced by exercise in these populations [33,34]. Therefore, among the therapeutic strategies introduced to alleviate inflammation in postmenopausal women, exercise seems to be an effective, safe, and accessible intervention [35-38].

In line with our results, Macedo Santiago et al. (2018) reported that eight weeks of resistance training is effective in reducing IL-6 levels in postmenopausal women [38-43] showed that long-term aerobic training with medium to high intensity (55% to 80% HR max), functional training and a combination of aerobic and resistance training are all influential in reduction of serum levels of IL-6 in this group of women [38,40-43] but in the studies conducted by Chen et al. (2018) and Arsenault et al. (2009) four weeks of kettlebell training and six months of aerobic training with low intensity (50% HR max) did not alter IL-6 levels significantly [44,45]. It seems reducing IL-6 levels by exercising in postmenopausal women

is sensitive to the duration and intensity of exercise.

To the best of our knowledge, this study is the first approach to the effects of BFR training on IL-6 levels in overweight postmenopausal women expressing low-intensity BFR training can decrease IL-6 levels as effectively as high-intensity traditional resistance training.

Based on our results, eight weeks of low-intensity BFR training can increase NRG-1 levels in overweight postmenopausal women as efficiently as high-intensity traditional resistance training. Neuregulin-1 is one of the epidermal growth factor family members that have significant roles in the development and plasticity of neurons, Myelin thickness, myocardial contractility, and generally in brain and heart health [46-49].

Animal studies show that exercise can improve cardiac functions, skeletal muscle growth, and glucose metabolism through NRG-1 pathways [50-52].

It is also stated that exercise can up-regulate NRG-1 expression to promote cardiac repair [53]. In the same way, LeBrasseur et al. elucidated that NRG family members, including NRG-1, are expressed in human muscle fibers to differentiate myocytes, and eight weeks of resistance training can elevate the receptor, erbB [54].

Unlike these findings, in a study by Froozandeh et al., the NRG-1 levels did not significantly change after eight weeks of neither aerobic nor resistance training, which can be due to insufficient intensity [55].

Our understanding is that this study is the first the only approach to analyzing the effects of BFR training on NRG-1 levels in overweight postmenopausal women, so there is undoubtedly a need for more research in this field to shed light on the efficacy of blood flow restriction training in this period of women's life.

CONCLUSION

In conclusion, we have identified that low-intensity BFR training and high-intensity traditional resistance training are functioning similarly on the levels of IL-6 and NRG-1 in postmenopausal women and low-intensity training with BFR is more effective than low-intensity traditional training in this proposition. Blood flow restriction by generating oxygen deficiency and activating different cellular pathways can be a beneficial training strategy to decrease inflammatory cytokines such as IL-6

and induce secretion and expression of repairing factors like NRG-1 for women after menopause.

Moreover, since high-intensity traditional resistance training contains heavyweights that can cause too much pressure on joints, it may be advantageous for post-menopausal women to apply BFR training which has been shown to bear similar effects as high-intensity training.

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Conflict of interest

The authors declare there is no conflict of interest

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ΑΝΑΣΚΟΠΗΣΗ

Η επίδραση της άσκησης BFR στα επίπεδα των των κυτοκινών NRG-1 και IL-6 σε υπέρβαρες μεταεμμηνοπαυσιακές γυναίκες

Zeinab Rezaee¹, Seyed Ali Akbar Hashemi Javaheri¹, Amir Rashidlamir¹, Onur Oral², Evangelia Stavropoulos³

¹Faculty of Sport Sciences, Ferdowsi University of Mashhad, Mashhad, Iran, ²Ege University, Faculty of Sports Sciences, Izmir, Turkey, ³Master of Research in Information and Communication, University of Lorraine, France

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η εμμηνόπαυση είναι μια αξιοσημείωτη περίοδος στη ζωή των γυναικών που συνοδεύεται από ορισμένες σωματικές και ψυχολογικές αλλαγές οι οποίες με τη σειρά τους οδηγούν σε παθήσεις όπως η παχυσαρκία, το υπερβολικό βάρος, τα καρδιαγγειακά και άλλες φλεγμονώδεις ασθένειες.

Σκοπός: Λόγω της σημασίας της υγειονομικής περιθάλψης σε αυτήν την περίοδο και της αποτελεσματικότητας της άσκησης στο να αμβλύνει τα εν λόγω συμπτώματα, σκοπός μας ήταν να συγκρίνουμε τα αποτελέσματα ενός αναδυόμενου εργαλείου άσκησης όπου περιορίζεται η ροή του αίματος στα άκρα χρησιμοποιώντας δύο κυτοκίνες που σχετίζονται με τη δημόσια υγεία, την IL-6 (Ιντερλευκίνη-6) και NRG-1 (Neuregulin-1) με εκείνα που προκύπτουν με την παραδοσιακή άσκηση, σε υπέρβαρες μεταεμμηνοπαυσιακές γυναίκες.

Υλικά-Μέθοδοι: 30 υπέρβαρες μεταεμμηνοπαυσιακές γυναίκες χωρίστηκαν τυχαία σε ομάδες BFR (Blood Flow Restriction), HI (High Intensity), LI (Low Intensity) (n=10) και πραγματοποίησαν οκτώ εβδομάδες ταυτόχρονης άσκησης τρεις ημέρες την εβδομάδα. Δύο ασκήσεις στο κάτω και δύο στο πάνω μέρος του σώματος με φόρτιση 20% 1RM (20% της μέγιστης μίας επανάληψης) για ομάδες BFR και LI και σε φόρτιση 80% 1RM (80% της μέγιστης επανάληψης) για ομάδα HI, επιπλέον των 20 λεπτών αεροβικής άσκησης στο τέλος. Τα επίπεδα IL-6 και NRG-1 μετρήθηκαν πριν και μετά τις οκτώ εβδομάδες προπονήσεων.

Αποτελέσματα: Διαφορές μεταξύ των ομάδων στα επίπεδα IL-6 παρατηρήθηκαν στις ομάδες BFR και HI (p=0,001 και στις δύο ομάδες) αλλά όχι στην ομάδα LI (p=0,29). Οι διαφορές μεταξύ των ομάδων ήταν σημαντικές μεταξύ BFR και LI (p=0,00) και HI και LI (p=0,007) αλλά όχι μεταξύ BFR και HI (p=0,11). Για τα επίπεδα NRG-1, παρατηρήθηκαν διαφορές στην ομάδα και στις τρεις ομάδες (p=0,001), (p=0,003), (p=0,007) και οι διαφορές μεταξύ των ομάδων για τα επίπεδα NRG-1 ήταν σημαντικές μεταξύ BFR και LI (p= 0,001) και HI και LI (p=0,038) αλλά όχι μεταξύ BFR και HI (p=0,065).

Συμπέρασμα: Η άσκηση χαμηλής έντασης BFR και η υψηλής έντασης, παραδοσιακή προπόνηση αντιστάσεων λειτουργούν παρόμοια στα επίπεδα IL-6 και NRG-1 σε μεταεμμηνοπαυσιακές γυναίκες και η προπόνηση χαμηλής έντασης με BFR είναι πιο αποτελεσματική από την παραδοσιακή προπόνηση χαμηλής έντασης σε αυτήν την πρόταση.

Λέξεις ευρετηρίου: άσκηση BFR, Nerogulin-1, NRG-1, Interleukin-6, IL-6, μεταεμμηνοπαυσιακές γυναίκες, Εμμηνόπαυση