Effects of Exercise Training on Postmenopausal Hypertension: Implications on Nitric Oxide Levels

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SUMMARY

Background: Postmenopausal hypertension is one of the leading causes of morbidity and mortality in women. Exercise training has been proved to decrease its risk factors and cardiovascular events. Aerobic exercise training stimulates endothelial nitric oxide release that acts as an antithrombotic and is cardiovascular protective. The effect of aerobic exercise training on postmenopausal hypertension is not fully elucidated.

The purpose of the study: to investigate the effects of moderate exercise training on nitric oxide levels in postmenopausal hypertension.

Methods: A prospective, randomized, controlled trial was conducted on 30 postmenopausal women involved in this study. The participants had at least one year's history of postmenopausal hypertension. Their ages ranged (40-50) years. Their body mass index ranged (30-36 Kg/m^2). They were divided into two equal groups (treatment and control). Nitric oxide levels and blood pressure were measured in both groups in the initial examination at the beginning of the study, and at the end of the study. The treatment group received moderate aerobic exercise training. This ranged from 60-70% of maximum heart rate by walking on a treadmill at an average speed of 4km/hour for at least 20 minutes, three sessions a week, for 8 weeks.

Results: Body mass index, systolic and diastolic blood pressures were statistically significantly decreased. Nitric oxide levels were significantly increased in the treatment group. In this group the level of NO increased by 30.4% and systolic blood pressure decreased by 16.2%. Diastolic blood pressure decreased by 9.5% and body mass index decreased by 6%. In the control group the NO level increased by 8%. Systolic blood pressure decreased by 3% and diastolic blood pressure decreased by 3%.

Conclusion: Exercise performed at moderate intensity for two months had obvious benefits in improving NO levels and controlling the hypertension in obese postmenopausal women.

KEY WORDS:
Nitric oxide, Aerobic exercise, Postmenopausal hypertension

INTRODUCTION

Nitric oxide or nitrogen monoxide (NO) or endothelium-derived relaxing factor (EDRF) is a binary molecule composed of nitrogen and oxygen atoms bound through covalent bonds. The metabolite has a molecular weight of about 30.0061 g/mol, it is actually a free radical [1]. Nitric oxide is a lipid soluble gas synthesized in endothelial cells of the blood vessels, from the amino-acid L-arginine, through the action of endothelial nitric oxide synthase [2]. It is released both naturally and in response to pharmacological stimulation by cardiovasodilators e.g. Nitroglycerin [3]. The endothelium of blood vessels uses NO to signal the surrounding smooth muscle to relax for vasodilatation and thus to increase blood flow. Nitric oxide (NO) also inhibits platelet aggregation and leukocyte adhesion to the vascular endothelium, thus preventing thrombus formation [4-6].

Impairment of the NO metabolic pathway is encountered in humans suffering from the disease spectrum of metabolic syndrome (diabetes, atherosclerosis, and hypertension) [7]. In the human body NO stimulates a series of successive reactions which end with phosphorylation of myosin light chain resulting ultimately in vascular smooth muscle relaxation, thus increasing blood flow [8].

Menopause occurs usually in women during the 40-50 year period of their life that is in their midlife. In obstetrical terms, it describes the permanent cessation of the primary functions of the ovaries to release hormones that cause the creation of the uterine lining, and its consequent shedding per menstrual cycle. It indicates the transition from a reproductive to a non-reproductive era of a woman's life [9]. The etiology of postmenopausal hypertension is complex and multi-factorial. A decrease in estrogen production with the consequent change in estrogen/androgen ratio is an important factor [10, 11]. Recent studies have indicated that the prevalence of hypertension in males of 30-45 years is higher than in females of a similar age, yet the prevalence in females after this age increases to levels similar to, or exceeds those in males [12-14]. Other factors causing a predisposal to postmenopausal hypertension are: endothelial dysfunction, oxidative stress, activation of the sympathetic nervous system and rennin-angiotensin-aldosterone system, biological composition changes in the female body and lack of physical activity [15-18].

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Epidemiological and experimental evidence supports the public health message that exercise/training and physical activity have substantial vascular and cardiac health benefits, with a 30% reduction in risk of cardiac disease [19]. Exercise/training is a well-established and potent physiological stimulus that reduces primary and secondary cardiovascular events. It also improves NO-mediated endothelial function in coronary and skeletal muscle arteries of large and small caliber. Given its importance in a number of atherogenic processes, improvement in endothelial function may underlie some of the reduction in cardiovascular risk associated with exercise/training and physical activity [20]. Exercise increases elements of the endogenous antioxidant defense mechanism, it also increases the expression and activity of endothelial nitric oxide synthase resulting in an increase in NO levels [21]. Although the physiological and cardioprotective effects of exercise/training have previously been documented, the signaling mechanisms that mediate these effects have not been fully elucidated [22].

MATERIALS AND METHODS

Subjects and study design:

This study was performed in 2011 at the outpatient clinic of the Faculty of Physical Therapy, Cairo University. A prospective, randomized, controlled trial was conducted in thirty patients who initially were enrolled in this study.

All participants had experienced at least one year of postmenopausal hypertension. Their ages ranged from 40 to 50 years. Each of them gave written informed consent. Cairo University Review Board had approved the study. The sample had a Body Mass Index (BMI) ranged from 30 to 36 Kg/m^2. Their Blood Pressure (BP) ranged from 140-160 mmHg (systolic - SBP) over 90-100 mmHg (diastolic - DBP) as shown in table I. The participants were not on any postmenopausal hormone therapy such as estrogen (not a tradition among women in the Middle East). They had neither previous history of hypertension nor receiving any anti-hypertensive drugs. The individuals had no history of diabetes or any other pathology within the spectrum of metabolic syndrome.

Moreover, they had neither orthopedic nor neuromuscular disorders that could have interfered with the training program.

Randomization:

A computer-generated, simple randomization procedure was used to allocate patients to treatment group and to control group, the medics who measured the blood pressure and all other variables incorporated in this study were blinded as to the allocation of the participants to both groups (exercise and control).

Measurements:

At initial screening, body weight and height were measured, then BMI was calculated as weight in kilograms divided by the height in square meters (kg/m^2) [23]. Blood pressures were measured at the same time (around 09:00 am) to avoid variations caused by diurnal rhythm. A pulse-meter was used to monitor the arterial pulse rate in order to identify and control the intensity of exercise according to the following formula: maximum heart rate = 220 – age [24]. Moderate intensity exercise was applied in this study, which is 60% - 75% of maximum heart rate.

The pulse-meter was used continuously during every exercise session to ensure that exercise intensity did not exceed the set level determined. Serum NO levels were estimated exactly a day before starting the program and exactly one day after the end of the program. We have followed a restricted criteria for measuring serum levels of NO by the same device and kits (Total Nitric Oxide kit used in ELISA, R & D systems, Minneapolis, USA) for all the patients of both groups, taking into account the food intake that might affect serum NO levels.

Exercise Protocol:

The exercise program was performed as three sessions per week that was continued for 8 weeks, making the total number of sessions 24. The program consisted of three phases followed by a relaxation period. These phases were: 1- warming up phase, 2- conditioning stimulus phase, 3- cooling down phase.

The warming up phase consisted of gentle stretching exercises and low impact aerobic training for 5-10 minutes, followed by the conditioning stimulus phase in the form of walking on an electric treadmill at an average speed of 4Km/hour for at least 20 minutes, keeping the arterial pulse within the target heart rate. The third phase (cooling down) was a period of gentle stretching exercise coupled with deep breathing for 5-10 minutes. These phases were followed by a relaxation period of at least 5 minutes to ensure that all subjects re-entered the resting state without experiencing any adverse effects of the training.

Analysis of data:

Baseline and follow-up characteristics of the study groups are presented as mean ± SD.

The responses after exercise/training were compared with controlled group responses using Student's paired t-tests, presented in table I. All statistical analyses were performed by SAS Software version 8.2 (Cary, NC).

RESULTS

Study population:

Thirty patients were recruited in this study see figure 1. There were no baseline characteristic differences between the two groups at the beginning of the study. Five patients were excluded from the final analysis. In the treatment group three patients discontinued the study. The first one because of acute back pain and the second one did not provide a blood sample, and the third developed a chest infection at the time of final assessment. Two patients in the control group discontinued without reasonable cause.

Outcome:

There was significant improvement in BMI ($p < 0.009$), SBP ($p < 0.0001$), DBP ($p < 0.0001$) and NO ($p < 0.0001$) values of treatment group in comparison to the control group at the

Table I: Baseline parameters of the patients of both groups (treatment and control) at the beginning of the study

Parameters of the study	Treatment group Mean ± SD	Control group Mean ± SD
No. of Subjects	15	15
Age (years)	52.9 ± 2.6	52.7 ± 2.2
Weight (Kg)	85.6 ± 10.8	86.1 ± 11.2
Height (cm)	156.6 ± 0.6	154.7 ± 0.5
BMI (kg/ m2)	34.91 ± 3.5	33.83 ± 4.1
SBP (mmHg)	148 ± 5.6	154 ± 6.7
DBP (mmHg)	94 ± 4.1	95 ± 4.2
NO (µmol/L)	24.3 ± 0.9	23.7 ± 0.4

Data are presented as mean and standard deviation (± SD), no significant difference, $p > 0.05$
SBP = Systolic blood pressure; DBP = Diastolic blood pressure; NO = nitric oxide

Table II: Comparison between treatment and control groups at the end of the study

Parameters of the study	Treatment group Mean ± SD	Control group Mean ± SD	P value
No. of Subjects	12	13	---
BMI (kg/ m2)	32.8 ± 1.5	34.7 ± 1.8	P < 0.009
SBP (mmHg)	124 ± 5.6	145 ± 6.7	P < 0.0001
DBP (mmHg)	85 ± 5.4	95 ± 3.7	P < 0.0001
NO (µmol/L)	31.7 ± 0.7	26.4 ± 0.3	P < 0.0001

Data are presented as mean and standard deviation (± SD).
SBP = Systolic blood pressure, DBP = Diastolic blood pressure, NO = nitric oxide

end of the study as demonstrated in table II.

The body mass index:
The mean BMI value in the treatment group at pre-study phase was 34.91 Kg/m^2 and this decreased to 32.8 Kg/m^2 after 8 weeks of training. The decrease was statistically significant ($p < 0.001$) as shown in (figure 2, a).

Blood pressure:
The mean SBP and DBP values in the treatment group were reduced from 148mmHg to 124 mmHg and 94 mmHg to 85mmHg respectively at the end of the study, with a statistically significant difference ($p < 0.001$), see (figure 2, b and c).

Nitric oxide level:
After 8 weeks training there was an improvement in the NO level ($p < 0.001$) as presented in (figure 2, d). At the end of the program, the mean NO level in the treatment group was increased from 24.3 to 31.7 µmol/L.

DISCUSSION

The primary findings of this prospective, randomized, controlled trial indicate that 8-weeks of regular moderate exercise in obese postmenopausal hypertensive patients decreased BMI, SBP and DBP and increased the NO level ($p < 0.001$). These observations together confirm the protective effects of moderate exercise/training on the occurrence of cardiovascular events in these patients. The results obtained from this study also support the fact that physical exercise is a pivotal factor to decrease cardiovascular diseases generally. Moderate exercise training increases NO release from endothelium, which acts as a vasodilator that increases blood flow at the mean time, it lowers the blood pressure. Our results confirm the results obtained in previous studies [25]. In the current study NO levels increased in response to training by 30.4%, SBP decreased by 16.2%, DBP decreased by 9.5% and BMI decreased by 6% compared to the pre-study values of the same parameters in the treatment group. On the other hand values of the same parameters did not show any significant changes in the control group.

One plausible explanation for the above mentioned changes in the parameters measured is an increase of L-arginine transport that leads to increased platelet NO synthase activity, which in turn increases cyclic guanosine monophosphate (cGMP) levels to reduce platelet aggregation (a cardioprotective phenomenon). Moreover, exercise/training reduced plasma concentrations of fibrinogen (thrombosis element) and C-reactive protein (inflammation marker) [25, 26].

The impact of NO on hypertension:
The results obtained from this study after fulfillment of the training program indicated that blood pressure was decreased, indicating the protective function of moderate aerobic exercise against the development of hypertension in obese post menopausal women. These findings support the results of studies performed by Seals *et al.* [27, 28] who demonstrated that regular aerobic exercise can decrease blood pressure in postmenopausal hypertensive women. Although the maximal aerobic capacity, body weight and dietary intake did not change according to the results of this group, the blood pressure improved [27]. This improvement was attributed to the increased levels of endothelial NO [27, 28].

Actually NO is involved in the central regulation of sympathetic outflow in humans, meaning that both neuronal and endothelial NO synthesis may contribute to the regulation of vasomotor vascular tone [29]. Our study showed a significant decrease of body weight in the treatment group. The results concerning body weight agree with the conclusions of a randomized controlled trial which stated

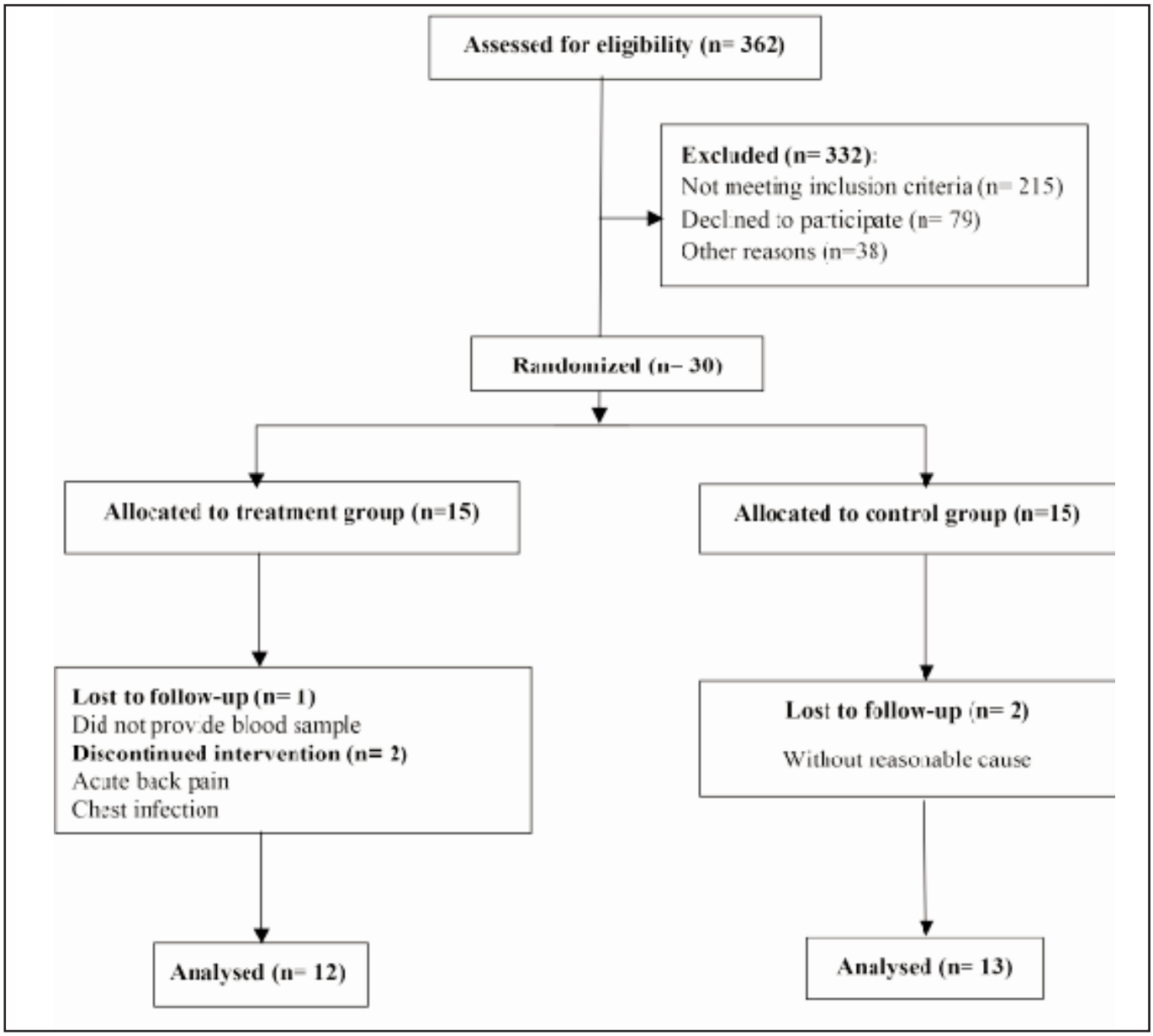

Fig. 1 : Flow diagram (chart) of patient disposition during the study

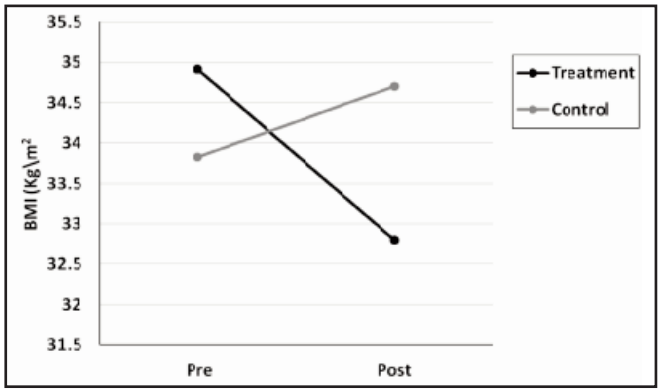

Fig. 2 : a: Mean values of the body index (BMI) in control and treatment groups
Comparison between mean values of body mass index in both groups at the beginning (pre) and at the end (post) of the study. The treatment group "

that regular exercise, such as brisk walking, results in reduced body weight and body fat among overweight and obese postmenopausal women [30, 31].

Our findings were supported by the results of another study that demonstrated that blood flow increase during exercise leads to higher intraluminal forces, which stimulate the release of vasodilator factors such as NO and prostacyclin by the endothelium [32]. The same study showed that walking lowers blood pressure in postmenopausal hypertension by 5 mmHg after 24 weeks of practice.

Clarkson *et al.* indicated that endothelium-dependant dilation in young men enhanced by aerobic exercise training was beneficial in preventing CV Diseases. These exercises maintain a high level of fitness, prevent age-related decline of microvascular NO-mediated vasodilator function, the

higher levels of NO confer anti-atherogenic benefit and prevent microvascular dysfunction in humans [33]. It is worth mentioning that regular moderate intensity exercise can be used to improve metabolic risk factors such as insulin and leptin levels in overweight/obese postmenopausal women [34]. Furthermore, exercise per se has been shown to be an important factor in the reduction of hypertension by decreasing the elevated activity of the sympathetic nervous system (SNS). According to Mueller, exercise may reduce the resting blood pressure and sympathetic outflow even in normal individuals [35]. It is important to point out that almost two decades ago two cohort studies also demonstrated that regular physical activity prevents the development of hypertension, moreover it has been found to lower the blood pressure in hypertensive individuals [36, 37].

Strengths and limitations of the study:
The supervised exercise training with this low drop rate strengthens the results gained from the current study. Although the sample chosen for this study is limited to sedentary, overweight or obese postmenopausal women, it represents a sizeable portion of the society that is likely to get benefits out of such exercise training. To our knowledge this study is limited since it lacks the assessment of study criteria of long-term follow up, because as has been stated before, the results of this study were obtained exactly after 8-weeks of exercise training.

CONCLUSION

Moderate aerobic exercise training promotes the reduction of risk factors of cardiovascular diseases in postmenopausal obese hypertensive women. The reduction in BMI and blood pressure, which occurs together with an increase in endothelial NO level, plays a pivotal role to protect against postmenopausal hypertension. Results of this work can be employed by clinicians to help postmenopausal women to overcome the increased risk of morbidities associated with menopause.

FUTURE PERSPECTIVES

Our next study on a similar group of participants will include the measurements of sex hormones (e.g. estrogen) and mineralocorticoids (aldosterone), pre and post-study in two groups (exercise and control). We believe that the global future research should focus on investigating the possibility of the administration of a NO preparation as a prophylactic measure for women with known risk factors of developing postmenopausal hypertension, in line with guidelines of the American Heart Association (AHA) [38].

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