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Influence of Oxidative Stress on Blood Pressure among Japanese Community-Dwelling Persons

Kawamoto R[1,2*], Ninomiya D[1,2], Kasai Y[2], Kusunoki T[2], Ohtsuka N[2], Kumagi T[1] and Abe M[1]

[1]*Department of Community Medicine, Ehime University Graduate School of Medicine, Ehime, 791-0295, Japan*

[2]*Department of Internal Medicine, Seiyo Municipal Nomura Hospital, Ehime, 797-1212, Japan*

[*]**Corresponding author:** Ryuichi Kawamoto, MD, PhD., Department of Internal Medicine, Seiyo Municipal Nomura Hospital, 9-53 Nomura, Nomura-cho, Seiyo-city, Ehime, 797-1212, Japan, Tel: +81-894-72-0180; Fax: +81-894-72-0938; E-mail:rykawamo@m.ehime-u.ac.jp

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Abstract

Introduction: Blood pressure (BP) is one of the most significant manifestations of aging and vascular disease. Oxidative stress is thought to be involved in the development of vascular dysfunction, however, the effect on baseline and changes in peripheral BP is unknown. We investigated whether baseline and changes in the oxidative stress marker, malondialdehyde-modified low density lipoprotein (MDA-LDL) are associated with baseline and change in BP, by a 12-week exercise among Japanese community-dwelling persons.

Methods: The subjects comprised 10 men and 76 women aged 70 ± 7 (range, 61-82) and 67 ± 7 (range, 53-81) years, respectively. Before and at the end of the 12-week training program, metabolic variables including MDA-LDL, and systolic BP (SBP) anddiastolic BP (DBP) were obtained.

Results: Gender, baseline TG, and MDL-LDL correlated significantly with baseline SBP; gender, age, BMI, TG, MDA-LDL, hsCRP, GGT, and HMA-IR correlated significantly with DBP. Stepwise linear regression analysis for baseline BP status showed that baseline BMI and MDA-LDL are significantly and independently associated with SBP, and age while baseline GGT significantly and independently associated with DBP. After the 12-week Nordic walking exercise, change in MDA-LDL significantly correlated with changes in SBP and DBP. Stepwise multivariate linear regression analysis for changes in BP parameters showed that reduction in MDA-LDL was significantly and independently associated with reduction in SBP.

Conclusions: These results suggest that reduction in MDA-LDL may be a predictor for reduction in SBP after a 12-week exercise in community-dwelling persons.

Keywords: Aging; Oxidized stress; MDL-LDL; Systolic blood pressure; Exercise; Community-dwelling persons

Introduction

Essential hypertension is a major cause of morbidity and mortality around the world. It is known for being a highly prevalent pathological condition for developing cardiovascular disease (CVD), including acute myocardial infarction and stroke. Despite the fact that mechanisms underlying hypertension are not yet fully understood, there is ample evidence demonstrating that oxidative stress is a key mechanistic mediator in its pathophysiology [1]. Oxidative stress results from an imbalance between generation of reactive oxygen species (ROS) and the antioxidant defense systems [2]. Recent studies indicate that increased oxidative stress is an important mediator of endothelial injury in the pathology of hypertension associated with increased production of pro-oxidants such as superoxide anion, hydrogen peroxide, decreased nitric oxide (NO) synthesis and a reduction in antioxidant bioavailability, which is the main factor responsible for maintaining vascular tone [3,4]. Results in humans are still less conclusive despite available data that involve oxidative stress as a causative factor of essential hypertension and possible therapeutic strategies that could prevent or treat this disorder [3,5].

Some studies have demonstrated an age-dependent increase in malondialdehyde (MDA) content, which is an end-product of radical-initiated oxidative decomposition of polyunsaturated fatty acids. It is therefore, frequently used as a biomarker of oxidative stress] and can play key roles in the progression of atherosclerosis [8,9]. We hypothesized that baseline and change in MDA-low density lipoprotein (MDA-LDL) as oxidative stress are associated with baseline and reduction in blood pressure {e.g., systolic blood pressure (SBP) and diastolic blood pressure (DBP)} resulting from the walking exercise, respectively.

To address this hypothesis, we investigated whether baseline and change in MDA-LDL are associated with each baseline and change in SBP by a 12-week Nordic walking exercise among Japanese community-dwelling persons.

Methods

Participants

The present study was designed as a part of the Nomura study (UMIN000010611) [10]. The study population was selected through a community-based annual check-up process at the Nomura health and welfare center in a rural town located in Ehime prefecture, Japan.

Participants were enrolled in the study by public health nurses at the health and welfare center. The physical activity level of subjects, information on medical history, present conditions, and medications were obtained by interview. Candidates with CVDs or any other major illnesses that could affect the laboratory test results were excluded. All individuals aged 53-82 years with a clinically documented diagnosis of hypertension, dyslipidemia, type 2 diabetes, obesity, or any combination thereof were identified from the case records. The study complies with the Declaration of Helsinki, and was approved by the ethics committee of Ehime University School of Medicine with written informed consent obtained from each subject.

Evaluation of risk factors

Information on demographic characteristics and risk factors was collected using the clinical files at baseline and at the completion of 12 weeks of training. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). We measured BP with an appropriate-sized cuff on the right upper arm of the subjects in the sedentary position using an automatic oscillometric BP recorder (BP-103i; Colin, Aichi, Japan) while they were seated after having rested for at least 5 min. The mean of two consecutive measurements was used for analysis. Triglycerides (TG), Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high sensitivity C-reactive protein (hsCRP), gamma-glutamyl transferase (GGT), and immunoreactive insulin (IRI) were measured during an overnight fast of more than 11 hours. Plasma hsCRP concentration was measured using a Behring BN II nephelometer and MDA-LDL (MDA-LDL) was measured using enzyme-linked immunosorbent assay. Homeostasis of model assessment of insulin resistance (HOMA-IR) was calculated from FPG and IRI levels using the following formula: {FPG (mg/dl) X IRI (mU/ml)}/405 [11].

Intervention

Participants were required to take part in three instructor led sessions per week lasting 120-minutes, for 12 weeks. Participants were issued poles and tutored on the correct technique for using the equipment during the first week, dedicating 120-minute sessions to the Nordic walking technique. The Nordic walking technique is a simple enhancement of normal arm swing when walking. The poles remain behind the body and pointing diagonally backward at all times. The pole length used for the Nordic walk was selected and adjusted to permit smooth arm motion, based on the INWA formula (0.68 × body height (in cm) [12], and to induce a near right-angle elbow flexion upon pole landing [13]. Assessment of post intervention dependent variables was performed within one week of the final walking session. Before and at the end of the 12-week intervention, functional tests and metabolic profiles were measured.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) unless otherwise specified, and for parameters with non-normal distributions (TG, MDA-LDL, hsCRP, GGT, HOMA-IR) the data are shown as median (interquartile range) values. In all analyses, parameters with non-normal distributions were used after log-transformation. Statistical analysis was performed using IBM SPSS Statistics Version 21 (Statistical Package for Social Science Japan, Inc., Tokyo, Japan). 12-week changes in various factors were calculated by subtracting the baseline values from the 12-week values. Differences among baseline and follow-up data were analyzed by paired t-test. Pearson's correlation coefficient and multiple linear regression analysis were used to estimate baseline and changes (follow-up value-baseline value) in MDA-LDL. A p-value<0.05 was considered significant.

Results

Overall, 86 participants (91%) completed the 12-week training program and health examination. The subjects comprised 10 men aged 70 ± 7 (range, 61-82) years and 76 women aged 67 ± 7 (range, 53-81) years. Baseline variables and the changes at 12 weeks are shown in Table 1. Participants had a mean body height of 152.4 ± 7.6 (range, 136.0-174.5) cm and a mean BMI of 24.5 ± 3.1 (range, 18.1-33.4) kg/m^2. Participants had several cardiovascular risk factors, and baseline BMI, LDL-C, HOMA-IR, SBP, and DBP were at the high end of the normal ranges. After the 12-week training program, BMI, HDL-C, MDA-LDL, hsCRP, HOMA-IR, SBP, and DBP decreased significantly, while TG, LDL-C, and GGT remained unchanged. The training program significantly reduced SBP and DBP by a mean of 5 and 2 mmHg, respectively.

Table 2 shows the relationships between baseline characteristics and BP parameters. Gender, baseline TG, and MDL-LDL correlated significantly with baseline SBP, and gender, age, BMI, TG, MDA-LDL, hsCRP, and GGT, while HMA-IR correlated significantly with DBP. Stepwise liner regression analysis for BP status shows that BMI and MDA-LDL are significantly and independently associated with SBP, while age and GGT are significantly and independently associated with DBP.

Characteristics N=86	Baseline	Follow-up	Change (⊿)	P-value*
Body mass index† (kg/m^2)	24.5 ± 3.1	23.5 ± 2.8	1.0 ± 0.8	<0.001
Triglycerides (mg/dL)	95 (66- (66 exercise training on BP (125)	94 (66-117)	2 ± 42	0.607
HDL cholesterol (mg/dL)	67 ± 16	65 ± 16	2 ± 7	0.005
LDL cholesterol (mg/dL)	130 ± 30	127 ± 31	4 ± 23	0.131
MDA-LDL (U/L)	72 (57-85)	67 (54-80)	5 ± 23	<0.001
High sensitivity CRP (mg/dL)	0.060 (0.030-0.113)	0.040 (0.020-0.093)	0.003 ± 0.134	0.045
γ-glutamyltransferase (IU/L)	17 (12-26)	17 (13-24)	0 ± 8	0.638

HOMA-IR	1.20 (0.79-2.11)	1.02 (0.66-1.52)	0.4 ± 0.9	0.002
Systolic blood pressure (mmHg)	138 ± 21	132 ± 18	5 ± 16	0.002
Diastolic blood pressure (mmHg)	75 ± 12	73 ± 12	2 ± 7	0.015

Change (⊿): follow-upbaseline data. HDL, high-density lipoprotein; LDL: Low-Density Lipoprotein; MDA-LDL: Malondialdehyde, Modified Low-Density Lipoprotein; CRP: C-reactive Protein; HOMA-IR: Homeostasis ModelAssessment of Insulin Resistance; Data for triglycerides, MDA-LDL, high sensitivity CRP, γ-glutamyltransferase and HOMA-IR were skewed, and are presented as median (interquartile range) values, and were log-transformedfor analysis; *P-value from paired t-test. Bold values indicate significance (p<0.05)

Table 1: Baseline and follow-up characteristics of participants.

	Systolic blood pressure		**Diastolic blood pressure**	
Baseline Characteristic N=86	**Pearson's correlation coefficient**	**Stepwise Multiple linear regression analysis**	**Pearson's correlation coefficient**	**Stepwise Multiple linear regression analysis**
	r (p-value*)	**β(p-value*)**	**r (p-value*)**	**β (p-value*)**
Gender (1=men, 2=women)	**-0.241(0.026)**	-----	**-0.081 (0.459)**	-----
Age	0.054 (0.624)	-----	**-0.343 (0.001)**	**-0.364 (<0.001)**
Body mass index	0.202 (0.063)	**0.206 (0.049)**	**0.292 (0.007)**	-----
Triglycerides	**0.255 (0.019)**	-----	**0.243 (0.025)**	-----
HDL cholesterol	0.154 (0.159)	-----	0.075 (0.493)	-----
LDL cholesterol	0.184 (0.091)	-----	0.147 (0.178)	-----
MDA-LDL	**0.283 (0.009)**	**0.271 (0.010)**	**0.261 (0.016)**	-----
High sensitivity CRP	0.192 (0.078)	-----	**0.263 (0.015)**	-----
γ-glutamyltransferase	0.171 (0.117)	-----	**0.358 (0.001)**	**0.376 (<0.001)**
HOMA-IR	0.211 (0.053)	-----	**0.350 (0.001)**	-----
R^2	-----	**0.126 (0.004)**	-----	**0.263 (<0.001)**

R: Pearson's correlation coefficient; β: Standardized coefficient, R^2: Coefficient of determination; *Adjusted for medication including antihypertensive, antidyslipidemic, and antidiabetic medication; Data for triglycerides, MDA-LDL, high sensitivity C-reactive protein, γ-glutamyltransferase, and HOMA-IR were skewed and log-transformed for analysis; Bold values indicate significance (p<0.05)

Table 2: Relationship between baseline characteristics and blood pressure parameters.

Table 3, shows and BP parameters. Change in MDA-LDL correlated significantly with change in SBP and DBP. Stepwise multivariate linear regression analysis was employed to evaluate the contribution of confounding factors for BP parameters. In this analysis, significantly and independently associated with

	⊿Systolic blood pressure		**⊿Diastolic blood pressure**	
Changes in Characteristics N=86	**Pearson's correlation coefficient**	**Stepwise Multiple linear regression analysis**	**Pearson's correlation coefficient**	**Stepwise Multiple linear regression analysis**
	r (p-value)	β (p-value)	r (p-value)	β (p-value)
Body mass index	0.140 (0.200)	-----	0.025 (0.821)	-----
Triglycerides	0.153 (0.161)	-----	0.092 (0.402)	-----
HDL cholesterol	0.193 (0.075)	-----	**0.392 (<0.001)**	**0.392 (<0.001)**
LDL cholesterol	0.028 (0.798)	-----	0.103 (0.345)	-----

MDA-LDL	**0.214 (0.048)**	**0.214 (0.048)**	**0.148 (0.175)**	-----
High sensitivity CRP	0.015 (0.894)	-----	0.037 (0.734)	-----
γ-glutamyltransferase	0.112 (0.303)	-----	0.203 (0.061)	-----
HOMA-IR	0.004 (0.972)	-----	0.005 (0.962)	-----
R^2	-----	**0.046 (0.048)**	-----	**0.154 (<0.001)**
r: Pearson's correlation coefficient; β: Standardized coefficient; R^2: coefficient of determination; (-----) did not remain in the final model by stepwise multiple linear regression analysis; Bold values indicate significance (p<0.05)				

Table 3: Relationship between changes in characteristics and blood pressure parameters.

Figure 1 shows the relationships between baseline characteristics and changes in MDA-LDL and BP parameters. Baseline MDA-LDL correlated significantly with both baseline systolic blood pressure (SBP) (r=0.289, p=0.007) and diastolic blood pressure (DBP) (r=0.253, P=0.019). After the 12-week Nordic walking exercise, change in MDA-LDL correlated significantly with change in SBP (r=0.214, P=0.048), but did not correlate with change in DBP (r=0.148, P=0.175).

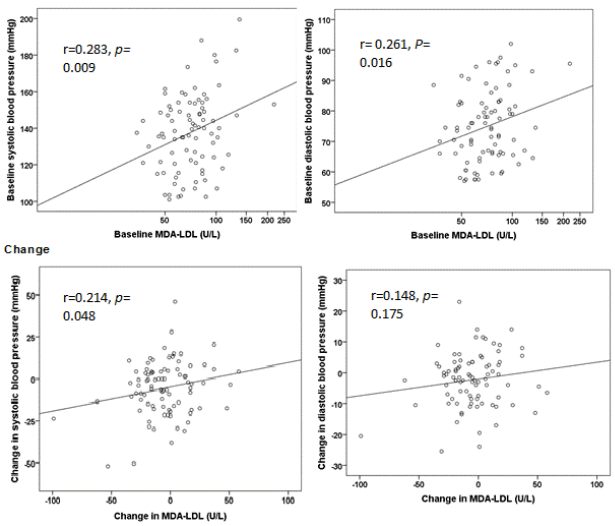

Figure 1: Correlation between malondialdehyde-modified low-density lipoprotein (MAD-LDL) and blood pressure status. Baseline MDA-LDL correlated significantly with both systolic blood pressure (SBP) (r=0.289, p=0.007) and diastolic blood pressure (DBP) (r=0.253, P=0.019); After 12-week Nordic walking exercise, change in MDA-LDL correlated significantly with SBP (r=0.214, P=0.048), but did not correlate with change in DBP (r=0.148, P=0.175).

Discussion

After the 12-week Nordic walking training program, metabolic variables and BP parameters improved significantly. Moreover, baseline and changes in MDA-LDL had direct and positive effects on SBP. Studies in elderly persons are generally few and controversial because of age-related differences in the effect of exercise training on BP [14]. To the best of our knowledge, this is the first study to have demonstrated that reduction in MDA-LDL induces reduction in SBP and may be a pathway by which exercise training improves cardiovascular health in elderly persons. This suggests that walking training is beneficial to cardiovascular health in elderly individuals.

There is growing evidence that increased oxidative stress and associated oxidative damage are mediators of vascular injury in cardiovascular pathologies, including hypertension and atherosclerosis [8,9,15]. Elevation of blood pressure in subjects with hypertension is accompanied by a marked increase in plasma and tissue lipid peroxidation products and an increase in MDA [15]. In comparison with 60 healthy subjects, 180 hypertensive patients had significantly higher plasma MDA levels (0.95 ± 0.28 versus 0.69 ± 0.21 μmol/l, p<0.001) and significantly lower levels of plasma ascorbic acid (34.83 ± 12.88 versus 51.76 ± 13.34 μmol/L, p<0.01) [16], whereas levels of serum nitric oxide and total anti-oxidant capacity were significantly decreased in all groups of essential hypertensive patients compared to the controls (p<0.001) [17]. In64 participants who do not exercise regularly and without any diabetic chronic complications, in parallel to 12 weeks of aerobic exercise (three times per week, n=31) and no exercise (control; n=33), exercise training favorably affected body weight, waist circumference, and blood pressure, and was associated with significant decrease in MDA levels [18]. In the present study, we found that baseline MDA-LDL was significantly associated with baseline SBP, and reduction in MDA-LDL after 12-week training was significantly and positively associated with reduction in SBP. Thus, Nordic walking training may protect against hypertension associated with oxidative stress. Reduction in SBP by a walking training exercise might be induced by reduction in MDA-LDL.

How can changes in MDA-LDL predict reduction in SBP after the 12-week Nordic walking training? Oxidative stress is considered to have occurred by a balance between a decrease in antioxidants or activity of non-enzymatic or enzymatic antioxidants and an increase in oxidation of non-enzymatic antioxidants [9]. A major benefit of moderate exercise is induction of mild oxidative stress that stimulates the expression of certain antioxidant enzymes [19,20]. Recently, Bergholm et al. [21] demonstrated that 12 weeks of intense physical training at 70% to 80% maximal oxygen uptake, consisting of four 1-hour running sessions per week, resulted in decreases in circulating antioxidants, such as alpha-tocopherol and beta-carotene, in healthy men. Physical exercise may acutely induce oxidative damage, although regular training appears to enhance antioxidant defense and has been shown to decrease lipid peroxidation in some animal studies. Aerobic exercise training can reduce oxidative stress by enhancing antioxidant defense mechanisms that include antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [22]. The results of our study demonstrated that Nordic walking training over 12 weeks is important for reducing parameters of oxidative stress. In

addition, aerobic exercise such as Nordic walking training improves weight loss with decreased waist circumference, insulin resistance [23] and glucose control [24]. These changes that occurred in our study might induce reduction in BP. Reduction in MDL-LDL, however, was associated with reduction in SBP, independent of change in confounding factors.

We must consider some limitations of this study. First, a 12-week program may potentially be too brief for evaluating the effects of walking training on BP parameters. Long-term studies of similar exercise intensity and frequency are warranted to elucidate whether Nordic walking may be a sustainable mode of exercise. Second, although we comprehensively adjusted for confounders such as gender, age, BMI, lipids, markers of inflammation (such as hsCRP), GGT, and HOMA-IR, in the association of BP parameters, other important measures such as markers of endothelial dysfunction were absent. Third, we could not eliminate possible effects of the underlying diseases and use of medication, especially antihypertensives and antidyslipidemics, on the results. Therefore the demographics and referral source may limit generalizability. These points need to be addressed again in a large population-based sample in a prospective manner.

In conclusion, the present study showed that baseline and changes in MDA-LDL had direct and positive effects on SBP. The underlying mechanism of this relationship is unclear, but it seems to be independent of traditional cardiovascular risk factors such as BMI, dyslipidemia, hsCRP, GGT, and HOMA-IR. Further prospective population-based studies are needed to investigate the mechanisms underlying this association.

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Author's Contributions

RK and DN participated in the design of the study, performed the statistical analysis and drafted the manuscript. RK, DN, YK, ToK, and TeK contributed to the acquisition of data and its interpretation. RK contributed to the conception and design of the statistical analysis. RK and MA conceived of the study, participated in its design, coordination and helped to draft the manuscript. All authors read and approved the manuscript.

References

1. Rodrigo R, Prat H, Passalacqua W, Araya J, Guichard C, et al. (2007) Relationship between oxidative stress and essential hypertension. Hypertens Res 30: 1159-1167.
2. Sinha N, Dabla PK (2015) Oxidative Stress and Antioxidants in Hypertension-A Current Review. Curr Hypertens Rev 11: 132-142.
3. Rodrigo R, González J, Paoletto F (2011) The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res 34: 431-440.
4. González J, Valls N, Brito R, Rodrigo R (2014) Essential hypertension and oxidative stress: New insights. World J Cardiol 6: 353-366.
5. Touyz RM, Briones AM (2011) Reactive oxygen species and vascular biology: implications in human hypertension. Hypertens Res 34: 5-14.
6. Marzani B, Pansarasa O, Marzatico F (2004) Oxidative stress and muscle aging: influence of age, sex, fiber composition and function. Basic Appl Mycol 14: 37-44.
7. Grune T, Berger MM (2007) Markers of oxidative stress in ICU clinical settings: present and future. Curr Opin Clin Nutr Metab Care 10: 712-717.
8. Orekhov AN, Bobryshev YV, Sobenin IA, Melnichenko A A, Chistiakov DA (2014) Modified low density lipoprotein and lipoprotein-containing circulating immune complexes as diagnostic and prognostic biomarkers of atherosclerosis and type 1 diabetes macrovascular disease. Intern J Mole Sci 15: 12807-12841.
9. Aviram M (1993) Modified forms of low density lipoprotein and atherosclerosis. Atherosclerosis 98: 1-9.
10. Kawamoto R, Kohara K, Katoh T, Kusunoki T, Ohtsuka N, et al. (2014) Effect of weight loss on central systolic blood pressure in elderly community-dwelling persons. Hypertens Res 37: 933-938.
11. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, et al. (2009) Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol 13: 621-630.
12. International Nordic Walking Federation (INWA) (2011) INWA Nordic Walking Portal.
13. Schwameder H, Roithner R, Muller E, Niessen W (1999) Knee joint forces during downhill walking with hiking poles. J Sports Sciences 17: 969-978.
14. Montain SJ, Jilka SM, Ehsani AA, Hagberg JM (1988) Altered hemodynamic during exercise in older essential hypertensive subjects. Hypertension 12: 479-484.
15. Gonick HC, Ding Y, Bondy SC, Ni Z, Vaziri ND (1997) Lead-induced hypertension: interplay of nitric oxide and reactive oxygen species. Hypertension 6: 1487-1492.
16. Wen Y, Killalea S, McGettigan P, Feely J (1996) Lipid peroxidation and antioxidant vitamins C and E in hypertensive patients. Ir J Med Sci 165: 210-212.
17. Hendre AS, Shariff AK, Patil SR, Durgawale PP, Sontakke AV, et al. (2013) Evaluation of oxidative stress and anti-oxidantstatus in essential hypertension. J Indian Med Assoc 111: 377-378, 380-381.
18. Jafri MS (2014) Effect of Aerobic Exercise Training on MDA and TNF-α Levels in Patients with Type 2 Diabetes Mellitus. Int Sch Res Notices.
19. Ji LL, Gomez-Cabrera MC, Vina J (2006) Exercise and hormesis: activation of cellular antioxidant signaling pathway. Ann N Y Acad Sci 1067: 425-435.
20. Gomez-Cabrera MC, Domenech E, Viña J (2008) Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radic Biol Med 44: 126-131.
21. Bergholm R, Makimattila S, Valkonen M, Liu ML, Lahdenperä S, et al. (1999) Intense physical training decreases circulating antioxidants and endothelium-dependent vasodilation in vivo. Atherosclerosis 145: 341-349.
22. Ji LL (1999) Antioxidants and oxidative stress in exercise. Proc Soc Exp Biol Med 222: 283-292.
23. Kawamoto R, Katoh T, Kohara K, Miki T (2015) Determinants of change in insulin resistance response to Nordic walking in community-dwelling elderly women. J Clin Gerontlo Geriatrics 6: 100-105.
24. Hagner-Derengowska M, Kałużny K, Kochański B, Hagner W, Borkowska A, et al. (2015) Effects of Nordic Walking and Pilates exercise programs on blood glucose and lipid profile in overweight and obese postmenopausal women in an experimental, nonrandomized, open-label, prospective controlled trial. Menopause 22: 1215-1223.