DOI: https://doi.org/10.5114/pm.2023.127902

Menopause Rev 2023; 22(2): 59-63

ORIGINAL PAPER

The pathogenic pathways of cardiovascular disease in perimenopausal women

Igor Lakhno, Sergei Korovai, Tetiana Struk, Svitlana Pak

Department of Obstetrics and Gynecology, Kharkiv National Medical University, Kharkiv, Ukraine

Abstract

Introduction: Menopause is associated with disturbed cardiovascular health. The objective of the study was to compare the effect of hormonal replacement therapy (HRT) and its combination with diet, L-arginine, and xylitol solutions on metabolic processes and cardiovascular health in perimenopausal women.

Material and methods: In total 106 women were enrolled in the cross-sectional study. The 36 patients of Group II received HRT. 35 women who had been prescribed additionally to HRT a diet, L-arginine, and also xylitol were included in Group III. 35 healthy reproductive-aged women were included in Group I (control). The variables body mass index (BMI), heart rate (HR), blood pressure (BP), lipid and carbohydrate metabolism and C-reactive protein, and menopausal Cooperman's score were determined before and after the 3-month program.

Results: The obtained results showed the homogeneity of average age, BMI, HR, BP, and Cooperman's score in Group II and Group III before inclusion in the study. But several variables changed significantly after a 3-month period. The study showed the effect of the 3-month program on BMI and Cooperman's score. We also found the restoration of the lipid profiles in Group III. The patients of perimenopausal age featured elevated levels of insulin and C-RP (C-reactive protein). The restoration of levels of insulin and CRP occurred in the process of the 3-month program.

Conclusions: The use of a 3-month program including diet, xylitol, and L-arginine solutions contributed to the reduction of Cooperman's score, chronic inflammation, and restoration of lipid and carbohydrate metabolism.

Key words: menopause, metabolic syndrome, cardiovascular disease.

Introduction

The problem of arterial hypertension is still of great significance. The human search for universal interventions to achieve longevity lies in the field of translational medicine. The fetal programming hypothesis explains the origin of metabolic syndrome, atherosclerosis, and cardiovascular disease [1]. No evident markers of disturbed vascular structure in women before the onset of menopause were found [2]. Thus, the decreased level of estrogens could be a trigger for endothelial malfunction and vasoconstriction.

The use of hormonal replacement therapy (HRT) is well known [3]. But some negative estrogen- or progesterone-dependent effects on women's health were detected [4–6]. The increased level of coronary heart disease or brain stroke found in some studies stimulates investigations in the field [7]. Thus, the additional prescription of medicines for endothelial protection could be a prospect for women in their perimenopausal years.

Metabolic disorders of the transitional age are associated with obesity. Physical activity, a diet, and some pharmacological interventions could be appropriate options for the aging female population. The use of diet and L-arginine solutions were found to improve metabolic variables in obese patients [8–10]. Any diet could induce the feeling of hunger and psychological discomfort. The application of xylitol solutions is known to reduce this suffering and provide optimal carbohydrate metabolism [11]. The addition to HRT use of diet, L-arginine, and xylitol solutions could be a possible therapeutic strategy for life extension. This speculation was preliminarily tested in a 1-month program [12]. This research was designed to provide physicians with an efficient method to protect cardiovascular health and menopausal disorders in middle-aged women.

The study aimed to compare the effect of HRT and its combination with diet, L-arginine, and xylitol solutions on metabolic processes and cardiovascular health in perimenopausal women.

Material and methods

In total 106 women were enrolled in the prospective cross-sectional study. The reporting of the study was done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Corresponding author:
Igor Victorovich Lakhno, Department of Obstetrics and Gynecology No 3, Kharkiv National Medical University, Kharkiv, Ukraine, e-mail: igorlakhno71@gmail.com

Submitted: 03.09.2022
Accepted: 09.11.2022

guidelines [13]. The study protocol was approved by the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education. Perimenopausal women who had visited the outpatient department each year for a preventive check were recruited to the study. The eligible participants were informed about the methodology of the study, its aims, objectives, indications, and possible complications before inclusion in the study. All patients who met the inclusion criteria gave written informed consent to participate in the investigation. They have not received any drugs including antihypertensives. The exclusion criteria were preexisting medical disorders such as diabetes mellitus type I, diabetes mellitus type II, thyrotoxicosis, rheumatic disease, malignancy, etc. The study was carried out among patients of the outpatient department of Kharkiv Municipal Perinatal Center between 1 June 2021 and 31 August 2021.

The 71 perimenopausal aged women were divided into two groups. The 36 patients of Group II received HRT. Sequential or continuous combined HRT was prescribed in patients with or without periods [5]. 35 women who had been prescribed additionally to HRT a diet, L-arginine infusions 200.0 ml once daily for a week, and 20 ml of oral L-arginine solution for 3 weeks, and also xylitol solution 200.0 ml once daily during the first 5 days of treatment were included in Group III. A low-carbohydrate and mild-fat diet (less than 26% carbohydrates or less than 130 gm/day) was used in the study [14–17]. The distribution of the nutrients was 20% of carbohydrates, 40% fat, and 40% protein. This diet featured a low glycemic index, slow ketogenesis, and anti-atherogenic effects [18]. The choice of such dosage and method of administration was made due to the bioavailability and fast therapeutic effect of L-arginine and xylitol [19, 20]. 35 healthy reproductive-aged women were included in Group I (control). They did not receive any diet or medications.

The variables body mass index (BMI), heart rate (HR), blood pressure (BP), and menopausal Cooperman's score were determined before and after the 3-month program. Biochemical studies were performed in the Sinevo laboratory on a Cobas 6000 analyzer (Roche Diagnostics, Switzerland) before and after the 3-month interval. All the study population was tested for serum triglycerides (TG), total cholesterol (CHC), high-density lipoprotein cholesterol (HDL cholesterol), low-density lipoprotein cholesterol (LDL cholesterol), and very-low-density cholesterol (VLDL cholesterol). The concentrations of TG and CHC were studied by the colorimetric enzymatic method and HDL cholesterol was investigated by the colorimetric enzymatic method with pre-precipitation of LDL cholesterol and chylomicrons. The atherogenic index, which reflects the ratio of atherogenic (CHD and LDL cholesterol) and antiatherogenic (HDL cholesterol) fractions of cholesterol, was also calculated. The levels of glycemia and insulin on an empty stomach were detected with subsequent calculation of the HOMA index. C-reactive protein (C-RP) as a marker of chronic inflammation was investigated.

Statistical analysis was performed with the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) program. The results thus obtained were analyzed with Student's *t*-test to compare data between groups. The significance was set at p-value < 0.05. For the statistical analysis of the relationship between X and Y, the correlation coefficients were estimated with Spearman's test.

Limitations of the study

A larger study population and a prolonged period of observation could contribute to a better outcome.

Compliance with ethics requirements

Ethical approval was obtained from the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education (registration number 0116U002865/30.05.2021).

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Results

The obtained results showed the homogeneity of average age, BMI, HR, BP, and Cooperman's score in Group II and Group III before inclusion in the study (Table 1). But several variables changed significantly after a 3-month period. The BMI values did not show statistically significant differences except in Group I and Group III after 3 months of observation. The hemodynamic variables did not change significantly in Group II and Group III. But Cooperman's score changed in Group III and showed similarity with Group I. Thus, the study showed the effect of the 3-month program on BMI and Cooperman's score.

The results of the study revealed atherogenicity in Group II and Group III before the start of the program (Table 2). Increased levels of TG, TCH, LDL, VLDL, and decreased concentration of HDL were detected in perimenopausal women before inclusion in the study. Therefore, AI was elevated in Group II and Group III. The changes in the levels of TG, TCH, LDL, VLDL, HDL, and AI contributed to the restoration of the lipid profiles in Group III. These variables were not significantly different between Group I and Group III. Thus, the use of diet, xylitol, and L-arginine solutions could be an ef-

Table 1. The variables average age, body mass index, heart rate, blood pressure, and Cooperman's score in the study population

Parameters, units of measure	Group I	Group II		Group III	
		Before onset	3 months later	Before onset	3 months later
Average age (years)	37.8 ±5.1	52.4 ±4.6 $p = 0.0371$	–	53.2 ±4.9 $p = 0.0329$	–
BMI	24.1 ±4.3	38.9 ±6.0 $p = 0.0489$	36.5 ±4.1 $p = 0.0406$	38.7 ±5.8 $p = 0.0471$	30.2 ±4.7 $p = 0.3417$
HR	71.6 ±8.8	85.4 ±11.2 $p = 0.3360$	83.5 ±10.4 $p = 0.4063$	87.2 ±12.5 $p = 0.3111$	78.2 ±9.3 $p = 0.6079$
Systolic BP [mm Hg]	114.6 ±16.3	138.7 ±19.4 $p = 0.3449$	135.2 ±14.9 $p = 0.3542$	139.8 ±17.3 $p = 0.2928$	128.3 ±14.2 $p = 0.5284$
Diastolic BP [mm Hg]	72.2 ±9.0	96.1 ±14.5 $p = 0.1659$	91.7 ±11.6 $p = 0.1885$	95.8 ±16.3 $p = 0.2136$	82.6 ±10.3 $p = 0.4497$
Cooper-man's score	5.2 ±1.3	28.6 ±7.4 $p = 0.0026$	19.4 ±5.1 $p = 0.0087$	29.3 ±8.2 $p = 0.0050$	10.1 ±5.4 $p = 0.3808$

BMI – body mass index, BP – blood pressure, HR – heart rate

Table 2. Biochemical parameters in the study population

Parameters, units of measure	Group I ($n = 35$)	Group II ($n = 35$)		Group III ($n = 36$)	
		Before onset	3 months later	Before onset	3 months later
TG [mmol/l]	1.16 ±0.22	1.75 ±0.56* $p < 0.0001$	1.37 ±0.45* $p = 0.0156$	1.78 ±0.43 $p < 0.0001$	1.20 ±0,25 $p = 0.4771$
TCH [mmol/l]	4.61 ±1.03	6.08 ±1.15* $p < 0.0001$	5.52 ±0.84* $p = 0.0001$	6.02 ±1.19* $p < 0.0001$	4.88 ±1.04 $p = 0.2790$
HDL [mmol/l]	1.79 ±0.38	1.59 ±0.41* $p = 0.0367$	1.60 ±0.42* $p = 0.0498$	1.56 ±0.34* $p = 0.0090$	1.65 ±0.38 $p = 0.1252$
LDL [mmol/l]	2.35 ±0.41	2.85 ±0.77* $p = 0.0012$	2.80 ±0.62* $p = 0.0006$	2.90 ±0.70* $p = 0.0001$	2.60 ±0.68 $p = 0.0658$
VLDL [mmol/l]	1.12 ±0.25	1.66 ±0.45* $p < 0.0001$	1.77 ±0.29* $p < 0.0001$	1.62 ±0,39* $p < 0.0001$	1.21±0.34 $p = 0.2091$
AI	1.60 ±0.41	2.82 ±0.53* $p < 0.0001$	2.71 ±0.61* $p < 0.0001$	2.80 ±0.61* $p < 0.0001$	1.78 ±0.45 $p = 0.0828$

AI – atherogenic index, HDL – high-density lipoprotein cholesterol, LDL – low-density lipoprotein cholesterol, TCH – total cholesterol, TG – triglycerides, VLDL – very-low-density cholesterol

* The differences were statistically significant compared to Group I ($p < 0.05$).

Table 3. Variables of carbohydrate metabolism and C-reactive protein in the study population

Parameters, units of measure	Group I ($n = 35$)	Group II ($n = 35$)		Group III ($n = 36$)	
		Before onset	3 months later	Before onset	3 months later
Glucose [mmol/l]	5.18 ±0.44	5.64 ±0.88 $p = 0.641630$	5.43 ±0.62 $p = 0.743307$	5.68 ±0.72 $p = 0.555443$	5.26 ±0.51 $p = 0.905808$
Insulin [IU]	5.59 ±0.62	12.60 ±3.1 $p = 0.029994$	12.34 ±3.1 $p = 0.036410$	12.66 ±3.2 $p = 0.033633$	7.10 ±2.2 $p = 0.511081$
HOMA index	2.28 ±0.46	3.31 ±0.43 $p = 0.106583$	3.14 ±0.42 $p = 0.171976$	3.29 ±0.54 $p = 0.159075$	2.63 ±0.31 $p = 0.530179$
CRP [mg/l]	2.35 ±0.30	4.13 ±0.51 $p = 0.003698$	4.02 ±0.68 $p = 0.027943$	4.18 ±0.73 $p = 0.023425$	2.83 ±0.44 $p = 0.370590$

CRP – C-reactive protein

The differences were statistically significant compared to Group I ($p < 0.05$).

fective intervention contributing to vascular health in average-aged women.

Changes in carbohydrate metabolism in perimenopausal women were found (Table 3). The variables of glucose level and HOMA index did not show any statistically significant differences between all study groups. The insulin level was found to increase in Group II and Group III. But this parameter was similar in Group I and Group III without any statistically significant differences after 3 months. The level of CRP was elevated at inclusion in the study. But later on, this parameter was not different between Group I and Group III. Thus, the patients of per-

imenopausal age featured elevated levels of insulin and CRP. The restoration of these variables' concentration occurred during the 3-month program.

The investigation of a possible relationship between BMI and other variables revealed certain regularities. The results of Spearman's correlation indicated that there was a significant medium positive relationship between BMI and diastolic BP (r = 0.308, p = 0.018). A significant medium positive relationship between BMI and Cooperman's score was found in Spearman's test (r = 0.362, p = 0.022). The results of Spearman's test showed that there was a significant medium positive relationship between BMI and glucose level (r = 0.451, p = 0.003). A significant large positive relationship in Spearmen's test between BMI and CRP (r = 0.507, p = 0.001) was detected. Thus, the variable BMI was related to the regulation of hemodynamics, menopausal disorders, carbohydrate metabolism, and chronic inflammation. Spearman's test showed a medium positive relationship between HOMA index and LDL cholesterol levels (r = 0.323, p = 030). Therefore, insulin resistance could be involved in atherogenesis. The found correlations showed a triggering role of obesity in metabolic disorders.

Discussion

This study showed additional opportunities in the prevention of metabolic disorders in perimenopausal women. The relationship found between BMI and diastolic BP supported the pathogenic role of metabolic disorders in chronic hypertension [21]. Systemic atherogenic vasculopathy could be related to insulin resistance and chronic inflammation [22]. The proposed method for the support of vascular health showed its efficiency in the restoration of lipid and carbohydrate metabolism. The observed decrease in C-RP level demonstrated a possible modulating influence of L-arginine [23]. The very sound finding was the fact of Cooperman's score reduction in the process of diet, and the use of xylitol and L-arginine solutions. These interventions could enhance the effect of HRT.

Physical training is a popular intervention in anti-aging programs. A previous study revealed the role of additional physical activity in the reduction of insulin resistance in women with climacteric syndrome [24]. The diet is also known as a possible way to prevent metabolic disorders. The use of daily intake of vegetables was investigated in a study [25]. A diet including 400 g per day of vegetables contributed to a better lipid profile and provided a sufficient intake of energy. Weight loss is associated with the restoration of metabolites that are increased in obese and insulin-resistant women. The level of xylitol could be of use in the prediction of the response to diet. Lower baseline levels of xylitol were predictive of a greater decrease in BMI [26]. Deficiency of L-arginine was a marker of endothelial dysfunction during different stages of menopause [27]. The application of L-arginine solutions additionally to aerobic exercises in postmenopausal women decreased BP [8].

Since the effect of HRT on BP is multifactorial, the use of estrogens is not definitely understood [28]. Lower autonomic tone and increased arterial stiffness were found in postmenopausal women compared to male persons of a similar age [29]. The effects of estrogens depend on the peroxidation and endothelial function [30]. Thus, our findings emphasize the possible options for the prevention of atherogenicity. We found that the proposed 3-month program was a novel and efficient method for the protection of cardiovascular health in women. Weight gain was the main factor for insulin resistance, atherogenicity, and menopausal disorders. The use of diet, xylitol, and L-arginine improved metabolic processes and reduced menopausal disorders [12].

Conclusions

Body mass index in perimenopausal women was associated with BP, menopausal Cooperman's score, carbohydrate metabolism, and inflammatory response. The use of a 3-month program including diet, xylitol, and L-arginine solutions contributed to the reduction of Cooperman's score, chronic inflammation, and restoration of lipid and carbohydrate metabolism. We did not find any effect on hemodynamics.

Disclosure

The authors report no conflict of interest.

References

1. Hoyer D, Żebrowski J, Cysarz D, et al. Monitoring fetal maturation-objectives, techniques and indices of autonomic function. Physiol Meas 2017; 38: R61-R88.
2. Wu J, Zhou Q, Wei Z, Wei J, Cui M. Atherogenic index of plasma and coronary artery disease in the adult population: a meta-analysis. Front Cardiovasc Med 2021; 8: 817441.
3. Nappi R.E., Simoncini T. Menopause transition: a golden age to prevent cardiovascular disease. Lancet Diabetes Endocrinol 2021; 9: 135-137.
4. Grossman DC, Curry SJ, Owens DK, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. JAMA 2017; 318: 2224-2233
5. Zhang GQ, Chen JL, Luo Y, et al. Menopausal hormone therapy and women's health: an umbrella review. PLoS Med 2021; 18: e1003731.
6. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. JAMA 2020; 324: 369-380.
7. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. JAMA 2017; 318: 927-938.
8. Puga GM, de P Novais I, Katsanos CS, Zanesco A. Combined effects of aerobic exercise and l-arginine ingestion on blood pressure in normotensive postmenopausal women: a crossover study. Life Sci 2016; 151: 323-329.

9. Hu S, Han M, Rezaei A, Li D, Wu G, Ma X. L-arginine modulates glucose and lipid metabolism in obesity and diabetes. Curr. Protein Pept Sci 2017; 18: 599-608.
10. Szlas A, Kurek JM, Krejpcio Z. The Potential of L-arginine in prevention and treatment of disturbed carbohydrate and lipid metabolism – a review. Nutrients 2022; 14: 961.
11. Meyer-Gerspach AC, Drewe J, Verbeure W, et al. Effect of the natural sweetener xylitol on gut hormone secretion and gastric emptying in humans: a pilot dose-ranging study. Nutrients 2021; 13: 174.
12. Lakhno I. State of metabolic processes and ways to improve them in premenopausal women due to the life extension strategy. Rep Endocrinol 2021; 61: 51-54.
13. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guildelines for reporting observational studies. J Clin Epidemiol 2008; 61: 344-349.
14. Watts M, Hager M, Toner C. The art of translating nutritional science into dietary guidance: history and evolution of the Dietary Guidelines for Americans. Nutr Rev 2011; 69: 404-412.
15. Ebbeling CB, Swain JF, Feldman HA, et al. Effects of dietary composition on energy expenditure during weight loss maintenance. JAMA 2012; 307: 2627-2634.
16. Ebbeling CB, Feldman HA, Klein GL, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. BMJ 2018; 363: k4583.
17. Ford Ch, Chang Sh, Vitolins MZ. Evaluation of diet pattern and weight gain in postmenopausal women enrolled in the Women's Health Initiative Observational Study. Br J Nutr 2017; 117: 1189-1197.
18. Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D. The effect of low-fat and low-carbohydrate diets on weight loss and lipid levels: a systematic review and meta-analysis. Nutrients 2020; 12: 3774.
19. Tangphao O, Grossmann M, Chalon S, Hoffman BB, Blaschke TF. Pharmacokinetics of intravenous and oral L-arginine in normal volunteers. Br J Clin Pharmacol 1999; 47: 261-266.
20. Amo K, Arai H, Uebanso T, et al. Effects of xylitol on metabolic parameters and visceral fat accumulation. J Clin Biochem Nutr 2011; 49: 1-7.
21. An S, Ahn C, Jang J, et al. Comparison of the prevalence of cardiometabolic disorders and comorbidities in Korea and the United States: analysis of the national health and nutrition examination survey. J Korean Med Sci 2022; 37: e149.
22. Zhang H, Sun T, Cheng Y, et al. Impact of metabolic syndrome and systemic inflammation on endothelial function in postmenopausal women. Turk Kardiyol Dern Ars 2022; 50: 57-65.
23. Mirhafez SR, Hariri M. L-arginine effect on inflammatory mediators: a systematic review of randomized controlled clinical trials. Int J Vitam Nutr Res 2021; 91: 562-570.
24. Proietto J. Obesity and weight management at menopause. Aust Fam Physician 2017; 46: 368-370.
25. Sari IK, Utari DM, Kamoshita S, et al. Increasing vegetable intake 400 g/day to control body weight and lipid profile in overweight hyperlipidemia menopausal women. J Public Health Res 2020; 9: 1733.
26. Geidenstam N, Al-Majdoub M, Ekman M, et al. Metabolite profiling of obese individuals before and after a one year weight loss program Observational Study. Int J Obes (Lond) 2017; 41: 1369-1378.
27. Klawitter J, Hildreth KL, Christians U, et al. A relative L-arginine deficiency contributes to endothelial dysfunction across the stages of the menopausal transition. Physiol Rep 2017; 5: e13409.
28. Srivaratharajah K, Abramson BL. Hypertension in menopausal women: the effect and role of estrogen. Menopause 2019; 26: 428-430.
29. Dela Justina V, Miguez J.S.G., Priviero F., et al. Sex Differences in Molecular Mechanisms of Cardiovascular Aging. Front Aging. 2021; 2: 725884.
30. Xiang D., Liu Y, Zhou S, Zhou E, Wang Y. Protective effects of estrogen on cardiovascular disease mediated by oxidative stress. Oxid Med Cell Longev 2021; 2021: 5523516.