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The effects of moderate-intensity step-aerobics, spinning, and educational game exercise programs on plasma dopamine and oxytocin levels in women in the menopausal transition period

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Ethics Committee Approval
Ethics Committee approval was obtained from the Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (Date: December 24, 2020, No: 2020/81).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Menopausal transition (MT) is defined as the transition from reproductive to post-reproductive life. Oxytocin has beneficial effects on health problems, such as sexual activity disorder, vaginal atrophy, cardiovascular system diseases and acceleration in bone mass loss, which may develop due to changes in reproductive hormone levels during the MT period. During exercise, which can be used as adjuvant therapy for most of these health problems, a temporary increase in catecholamine levels is required for response to exercise-induced stress. However, the effects of exercise programs applied during the MT period on plasma dopamine (pDA) and plasma oxytocin (pOT) levels are unknown. The aim of this study was to investigate the effects of three different types of exercise on plasma dopamine (pDA) and plasma oxytocin (pOT) levels in sedentary women in the MT period.
Methods: Twenty-six sedentary healthy participants in the MT period whose fitness levels in the standard maximal exercise treadmill test were at a level that would complement the exercise programs in our study, were included in the study. Participants with the following conditions were excluded from the study: physical disability that would not allow exercise, systemic disease, unilateral oophorectomy, or history of smoking. In addition, participants who could not complete any of the exercise programs for any reason were excluded from the study. Three different exercise programs at moderate intensity [maximum heart rate (HR) = 50%-60%] of 60 minutes duration were performed by the participants at one-week intervals: (i) step-aerobics (SA), (ii) spinning (SP) and (iii) station work in the form of recreational educational games (EG). pOT and pDA levels were measured using the enzyme-linked immunosorbent assay method in venous blood samples taken from participants before the exercise and during the last five minutes of the exercise. pOT and pDA levels measured before the exercise and in the last five minutes of the exercise were compared.
Results: The median age was 45 (41-45) and the body mass index (BMI) was 29 (27-34). There was a significant increase in mean pDA levels during exercise compared to pre-exercise in all three activities of moderate-intensity, SA, SP, and EG ($P = 0.008$, $P = 0.001$ and $P = 0.030$, respectively). The mean pOT level increased significantly during moderate-intensity SA and EG ($P = 0.003$ and $P = 0.001$, respectively). When the relationships between pDA and pOT levels and the variables of age, BMI, pulse rate, and maximum HR during all three exercises were evaluated, there was a significant positive correlation between pOT levels and maximum HR only during EG ($r = 0.439$, $P = 0.028$).
Conclusions: This study showed that SA and EG applied in women in the MT period increased both pDA and pOT levels, while SP only increased the pDA level significantly. Therefore, SA and EG exercises can contribute positively to the quality of life of women with health problems due to low pOT levels during the MT period.

Keywords: Menopausal transition period, Woman, Exercise, Dopamine, Oxytocin

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Introduction

Menopausal transition (MT) is defined as the transition from reproductive to post-reproductive life [1], and the average duration of the MT period is approximately four years [2]. During this period, depending on the changes in reproductive hormonal patterns, various changes including vasomotor and genitourinary symptoms, mood, temporary cognitive function and sleep disorders, decrease in sexual desire, and increase in bone absorption rate can be observed [1]. This period is also associated with the development of central adiposity [3]. Aerobic exercises (AEs), which are characterized by high repetition and low resistance demands during skeletal muscle contraction, play a homeostatic role in the regulation of energy production, blood flow, and substrate use in response to movement. They are also influential on obesity, coronary artery disease, Alzheimer's disease, and depression and anxiety disorders. Exercise can be used as adjuvant therapy for various diseases, such as osteoporosis and some types of cancer [4].

Dopamine (DA) is a member of the catecholamine family. In the synthesis of catecholamines, phenylalanine or L-tyrosine are sequentially converted to 3.4-dihydroxyphenylalanine (L-DOPA), DA, norepinephrine (NE) and epinephrine (E) by enzymatic biotransformation [5]. Although catecholamines are mainly produced in the adrenal medulla and postganglionic fibers of the sympathetic nervous system [5], DA cannot cross the blood-brain barrier [6] and approximately 50-90% of plasma DA (pDA) originates from sympathetic noradrenergic (sympathoneural) nerves [5]. Less than 2% of the total pDA is in free form, but free pDA concentration is approximately equivalent to E concentration and is around 20% of NE concentration [7]. DA has established roles in the regulation of cognitive functions in the central nervous system (CNS), in the control of movement and coordination [6], and in various tissues outside the CNS, including the cardiovascular system (CVS) and the endocrine pancreas [8]. Oxytocin (OT), a classical neuropeptide, is produced mainly in hypothalamic OT neurons, in extrahypothalamic brain regions, and scattered OT cells in peripheral regions [9]. Locally produced OT, in addition to its local effects, influences central and peripheral functions in relation to brain OT [10]. OT generally facilitates social cognition and behaviors, such as social memory, attachment, sexual activity, maternal behavior, inter-couple bonding and trust [9]. It also protects the CVS [10], exerts anabolic effects on bone tissue [11], and can reverse vaginal atrophy when applied topically [12].

Blood OT levels decrease gradually starting at middle age [11] and decreased OT secretion during aging can cause various health problems, including CVS diseases, osteoporosis, urinary incontinence, sexual dysfunction, obesity, and a decrease in postmenopausal metabolic rate [9]. During exercise, which can be used as adjuvant therapy for most of these health problems [4], a temporary increase in catecholamine levels is required for response to exercise-induced stress [5]. However, the effects of exercise programs applied during the MT period on pDA and pOT levels are unknown. This study aims to evaluate the effects of moderate-intensity exercise programs, including step-aerobics (SA), spinning (SP), and educational games (EG), on pOT and pDA levels during the MT period of sedentary women.

Materials and methods

This prospective study was conducted between March 1, 2021 and August 1, 2021, as a cooperative research between the Gynecology & Obstetrics and Medical Biochemistry Departments and the Sport Sciences Faculty at Niğde Ömer Halisdemir University. All study steps were carried out at the Training and Research Hospital of the same university. Local Ethics Committee approval was obtained before the study (Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee, Date: December 24, 2020, No: 2020/81).

Participants

Twenty-six healthy participants between the ages of 41-45 years who were in the MT period completed this study. Subjects were selected from women who applied to the NOHU Training and Research Hospital Gynecology and Obstetrics Polyclinic between March 1, 2021 and May 11, 2021.

A detailed anamnesis of all women with menstrual cycle disorders was taken in the Gynecology and Obstetrics Clinic, followed by physical and genital examinations, transvaginal ultrasonography, and diagnostic laboratory tests. Blood urea, creatinine, glucose, high-density lipoprotein, low-density lipoprotein, triglyceride, hemoglobin, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, and free thyroxine levels and blood pressure were measured in all participants who agreed to participate in the study. The Stages of Reproductive Aging Workshop plus Ten Simplified Bleeding Criteria were used to determine the menopausal status of women with menstrual cycle disorders. Early MT was defined as a persistent (recurring within ten cycles) difference of seven or more days in length of consecutive cycles. Late MT transition was defined as the occurrence of amenorrhea for 60 days or more, or detection of greater than 25 IU/L of follicle-stimulating hormone (FSH) in a randomly taken blood sample [13]. Physical inactivity was defined as insufficient physical activity (PA) level less than 150–300 minutes of moderate-intensity, or 75–150 minutes of vigorous-intensity PA, or some equivalent combination of moderate-intensity and vigorous-intensity aerobic PA per week [14]. The PA readiness questionnaire test [15] was administered to all participants to determine the safety or potential risks of exercise. In addition, the standard maximal graded exercise treadmill test [16] was applied to determine the fitness levels of the participants.

The study included healthy sedentary participants who were in the early or late MT period, did not have any diagnosed disease, did not receive medical treatment, did not actively engage in any sports, and whose fitness levels in the standard maximal exercise treadmill test were at a level that would complement the exercise programs in our study.

The following patients were excluded from the study: those with physical disability or systemic disease (cardiovascular, respiratory, musculoskeletal, metabolic-endocrine system, cancer and psychological disease) that would not allow exercise, malnutrition, anemia, ovarian pathology, oophorectomy, hysterectomy, medical treatment history, and a history of smoking. In addition, participants who could not continue the research for any reason or could not complete any of the exercise programs in our study were also excluded.

Protocols of exercise interventions

Before starting the exercise, the participants' height, weight, resting heart rate (HR) and blood pressure were measured. BMI (kg/m²) was calculated by dividing body weight (kg) by height squared (m2). Maximum HR was calculated by subtracting age from 220. The target HR of the participants was calculated according to the Karvonen formula: Target HR range = [resting HR + (maximum HR - resting HR) × exercise intensity%] [17].

The daily activities of the participants were restricted on the days in which the exercise programs were scheduled, but not on other days. Participants were subjected to 60-minute moderate-intensity (50-60% of maximum reserve HR) SA, SP, and EG exercise programs at one-week intervals under supervision. In each type of exercise, seven minutes of warm-up exercises were completed before starting the exercise, and five minutes of stretching and cooling exercises were performed to rest the muscles after the exercise was completed. The heart rate during exercise was determined by calculating the average heart rate, as recorded on a Polar watch (Polar S810i, Finland) every five minutes.

The step-aerobics exercise plan consisted of the following movements: 24 counts of march and step touch; 16 counts (each side) of step heel, step touch, toe touch, toe jack, heel jack, knee lift, leg curl, leg reach, grapevine, heel lift, soft jog, and basic step.

The spinning exercise plan comprised pedaling movements for 20 minutes each, by sitting (holding and clapping) and standing (climbing and sprinting position) according to the rhythm of the music.

Educational game and station plan: Since the educational games were in a competitive format, the participants were divided into two equally-sized groups, A and B. Following the hoop game (Hula Hoop), each participant performed five counts of the following: trunk curl on a mat, mounting and dismounting a bosu ball while standing, rope jumping, and slalom movement. The educational games were completed by touching a pre-specified agility cone and then passing a hoop through the slalom bar once. Finally, the groups made a contest of popping the balloon on the chair for two minutes by sitting down.

Blood sample collection and measurement of oxytocin and dopamine levels in plasma

Before the exercise and during the last five minutes of the exercise, 5 ml of venous blood samples were taken from all participants in tubes with ethylenediaminetetraacetic acid, and plasma was obtained by centrifuging at 3000 rpm for ten minutes. The obtained plasma samples were stored at -80 °C until ELISA analysis. pDA and pOT levels were measured using ELISA kits (Cloud-Clone Corp., USA) according to the manufacturer instructions. The minimum detectable dose of OT (Catalog No: CEB052Ge) and DA (Catalog No: CEA851Ge) were typically less than 4.99 pg/mL and 4.71 pg/mL respectively. The intra-assay coefficient of variation (CV) and inter-assay CV for both OT and DA were < 10% and < 12%, respectively. Human DA and OT standard curve graphs were obtained by plotting the absorbance values obtained against their standard concentrations. The least squares method was used in this graph. Concentration values corresponding to the absorbance values determined from each sample were calculated by using the relevant correlation coefficient and the resultant linear equation.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Normal distribution was determined by examining the Shapiro-Wilk tests. If continuous data did not show normal distribution, descriptive statistics were provided with median and interquartile range values; whereas mean and standard deviation were used to describe data with normal distribution. When continuous variables were not normally distributed, comparisons of two dependent groups were performed using the Wilcoxon test, and when they were normally distributed, comparisons were performed with the paired samples t test. The Kruskal-Wallis test was used for intergroup comparisons to detect the differences in the amount of change in hormone levels during exercise. Spearman's correlation coefficients were calculated to determine directional relationships between continuous variables. Two-tailed *P*-values with an alpha significance level of less than 0.05 were considered statistically significant.

Results

The median age of the 26 women included in the study was 45 (41-45) years and subjects had a median BMI of 29 (27-34).

When the moderate-intensity SA, SP and EG exercise types were compared in terms of median HR and maximum HR before and during exercise, no significant difference was found (Table 1).

Table 1: Pulse rates before and after exercise programs

Exercise programs	Pulse rate		Maximum
	Before exercise Mean (SD) Median (min-max)	During exercise Mean (SD) Median (min-max)	Heart rate Mean (SD) Median (min-max)
Step-Aerobics	76.15 (2.89) 76 (70-84)	132.96 (1.93) 132 (130-136)	175.23 (1.27) 174 (174-178)
Spinning	75.02 (1.69) 75 (70-79)	123.77 (1.82) 123 (120-126)	174.73 (2.24) 175 (171-180)
Educational Game	75.81 (1.76) 75 (70-80)	138.88 (1.44) 140 (137-142)	172.77 (2.36) 172 (170-178)
P-value	0.94	0.065	0.96

SD: Standard deviation, min-max: The minimum and maximum values of the dataset

Compared with the mean plasma levels before exercise, there was a significant increase in mean pDA levels during all three exercise programs and in mean pOT levels during the EG and moderate-intensity SA programs (Table 2).

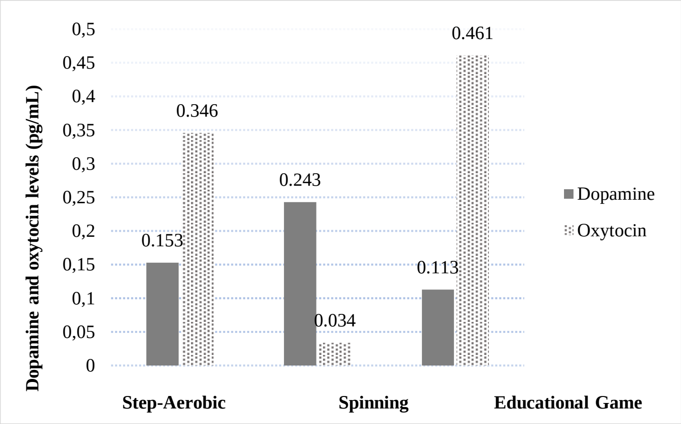
Table 2: Comparison of mean plasma dopamine and oxytocin levels (pg/mL) before and after step-aerobics, spinning, and educational game exercise programs

Hormones	Step-Aerobics Mean (SD)	Spinning Mean (SD)	Educational Game Mean (SD)
Dopamine			
Before Exercise	2.00 (0.19)	2.03 (0.15)	2.01 (0.17)
After Exercise	2.16 (0.31)	2.28 (0.29)	2.13 (0.19)
P-value	0.008	0.001	0.030
Oxytocin			
Before Exercise	2.16 (0.40)	2.66 (0.32)	2.04 (0.56)
After Exercise	2.51 (0.43)	2.69 (0.21)	2.50 (0.53)
P-value	0.003	0.808	0.001

SD: Standard deviation

Although pDA level increased during all three exercise programs, there was no significant difference between the three programs in terms of the amount of change in pDA (*P* = 0.083). The amount of increase in pOT level during exercise was found to be significantly higher in both the SA and EG groups compared to the SP group (*P* = 0.025), while levels were similar in the SA and EG groups (*P* = 0.714) (Figure 1).

Figure 1: The effects of moderate-intensity step-aerobics, spinning, and educational game exercise programs on plasma dopamine and oxytocin levels



When the relationships between pDA and pOT levels measured during exercise and age, BMI, pulse rate and maximum HR were evaluated, there was a significant positive correlation only between pOT levels during EG and maximum HR (r = 0.439, *P* = 0.028).

Discussion

In this study, the changes in pDA and pOT levels were investigated by applying moderate-intensity acute SA, SP and EG exercise programs to sedentary women in the MT period at one-week intervals. Our first important finding in the study was that all three exercise programs caused a significant increase in pDA level. Our second important finding was that SA and EG, which were the other two exercise programs apart from SP, caused a significantly greater increase in pOT levels.

The effect of exercise on pDA level has been investigated in several studies that differ in participant characteristics and methodological aspects [18-21]. In one study, an increase in plasma DA, NE and E levels was found in non-athlete healthy women in their 20s (compared to controls) after high-intensity standard team sports, light athletics, gymnastics, and outdoor runs performed with the interval method [18]. Another study found that there was a significant increase in plasma levels of DA, NE and E in participants with dilated cardiomyopathy with a mean age of 49.7 years after cardiopulmonary exercise (upright graded bicycle exercise) [19] A significant increase in urinary DA level four weeks after the application of bicycle ergometer exercise in participants aged 42-63 with essential hypertension has been reported [20]. Furthermore, in a study involving women with depression who were aged 18-65 years, exercise was found to significantly increase the pDA level compared to the control group (16 weeks of low-intensity warm-up, aerobics and low-intensity cooling down exercises); however, interestingly, plasma NE and E levels did not change [21]. In another study, it was found that NE and E concentrations in arterial and venous blood increased, but DA concentrations did not change after dynamic forearm exercises at submaximal and maximal intensities in healthy men [22]. Although comparison of our results with the literature was limited due to a lack of similarly designed studies, we found that there was a significant increase in pDA level after the application of moderate-intensity SA, SP, and EG exercises in sedentary women in the MT period. Interestingly, in a previous study, it was found that blood DA level did not change with dynamic forearm exercises at submaximal and maximal intensities [21], but increased in two other studies in which relatively larger muscle groups were activated, which was similar to the results found in our study [18, 19]. These findings suggest that the size of muscle groups activated during exercise may be related to the change in blood DA level.

The effect of acute exercise on pOT levels in healthy non-athletes was investigated in only one previous study involving nine participants aged 25-42 years [23]. In this study, a 20-minute treadmill run was planned with gradual increase of intensity until 90% of the maximum oxygen consumption (VO2) of each subject was reached in the last five minutes of the exercise. It was determined that the pOT concentrations did not change in either the early follicular phase or the midluteal phase of the menstrual cycle [23]. Another study reported that 11 weeks of lower-body pressure supported exercise, which was applied to obese non-diabetic women aged 18-56 years by use of 60% body weight for half an hour 2-3 times a week, had no effect on pOT concentrations [24]. When the effects of a maximum fatigue test, 60-minute treadmill and a 56-km ultramarathon, were evaluated among seven runners (five males and two females), the ultramarathon was found to be the only running exercise that caused a significant increase in pOT value [25]. It has also been reported that female athletes between the ages of 14-21 have lower nocturnal pOT levels compared to non-athletes [26]. When literature data are evaluated overall, it can be said that the effects of different types and intensities of exercise programs on pOT levels may vary depending on the age groups and fluctuating PA levels of participants. In our study, we found that the pOT level increased significantly during moderate-intensity SA and EG exercise programs in women in the MT period, but did not change during SP. Our findings show that, although different types of exercise performed among sedentary women in the MT period have similar duration and intensity, their effects on pOT levels may vary.

Adaptive changes that occur during exercise to meet the demands of increased metabolic rate include increased VO2, HR, and respiratory rate, altered blood flow to active muscles, secretion of stress hormones (e.g., adrenocorticotropic hormone, cortisol, catecholamines), and increased body temperature [27]. Conflicting results have been reported in studies evaluating the potential effects of DA on PA and exercise capacity in healthy participants. It has been reported that when DA infusion was given to male participants during exercise, breath-taking ventilation (VE), carbon dioxide production (VCO2) and oxygen consumption (VO2) did not change [28], but the VE / VCO2 slope decreased [29]. In studies in which DA inhibitor drugs were administered, it was found that the acute administration of a dual dopamine/noradrenaline reuptake inhibitor to athletes increased performance under hot conditions [30], while pulmonary gas exchange improved with DA receptor blockade in healthy young adults, but with decreased exercise performance [31]. Our study showed no significant correlation between pDA level and heart rate and maximum heart rate during the three exercises. Although it is not possible to determine whether there is a relationship between pDA level and exercise performance with these findings, our findings suggest that there may not be a direct relationship between pDA level and HR in women in the MT period.

Little is known about the role of OT in PA. One study determined that there was a positive correlation between fasting serum OT level and resting energy consumption in athletes, but this correlation was not found in non-athletes, and it was concluded that OT may play an important role in regulating energy intake and use, especially in determining an energy deficit [32]. In addition, it has been reported that OT increases stress-related oxygen consumption to facilitate muscle movement for active stress coping behaviors under stressful conditions [33, 34]. This can have a supportive role for various hormones (arginine vasopressin and atrial natriuretic peptide), which are known to have a role in the regulation of fluid balance, together with brain natriuretic peptide, under extreme physical stress conditions [25]. As a result, OT may cause cardiovascular effects through its effects on the central nervous system and with other mediators such as atrial natriuretic peptide, nitric oxide, and alpha 2-adrenoreceptors [35]. Our study observed that pOT levels increased significantly in both moderate-intensity SA and EG during exercise, but there was a positive and significant correlation between maximum HR and pOT level during EG. These findings suggest that, unlike SA, various mechanisms may be activated during EG, which may be influential on pOT levels and could have an effect on maximum HR.

Limitations

One of the limitations of our study is that we could not compare our findings with the literature due to methodological differences. Our study comprised female participants in MT, limiting the possibility of generalizing our findings to other populations. In addition, only pDA and pOT levels were measured both before and after exercise in our study. Therefore, the relationship between other hormones whose secretion can change with exercise and pDA or pOT could not be evaluated. In addition, once the participants were included in the study, their daily activities were restricted on the days of the exercise programs, but daily activities were not restricted on other days. Therefore, differences in baseline activities may have affected the results of the study.

More studies are needed to reveal the potential bidirectional relationships between acute or chronic exercise programs and pDA or pOT levels in women experiencing MT and the long-term clinical outcomes of these relationships.

Conclusion

This study showed that SA and EG applied in women in the MT period increased both pDA and pOT levels, while SP was only associated with a significant increase in pDA level. Therefore, SA and EG exercises that increase pOT levels might contribute positively to the quality of life of women with health problems, which may be a result of low pOT levels during the MT period.

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