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Effect of aerobic exercise with diet on sex hormones and selected coagulation biomarkers in obese postmenopausal women: a randomized clinical trial

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Abstract. – OBJECTIVE: The current study determined the effect of aerobic training and diet program versus diet only on sex hormones and selected coagulation biomarkers in obese postmenopausal women. Further, the correlation between the measured variables after the intervention was identified.

PATIENTS AND METHODS: Eligible 40 women were distributed into two equal groups: the experimental group that received aerobic training three times per week for 12 weeks along with a balanced diet, and the control group that received a balanced diet only. Changes in weight, body mass index, sex hormones, and coagulation biomarkers were assessed pre-and post-intervention. The correlation between evaluated variables was assessed.

RESULTS: Both groups demonstrated a significant difference in sex hormones (i.e., a substantial decrease in estradiol, total testosterone, free testosterone, and a substantial increase in sex hormone-binding globulin) and coagulation biomarkers (a considerable reduction in plasminogen activator inhibitor-1 activity, fibrinogen, and a significant increase in tissue plasminogen activator, prothrombin time, and cephalin-kaolin coagulation time). This discrepancy was highly significant in the experimental group ($p < 0.01$) relative to the control group ($p < 0.05$), and there was a strong link between sex hormones and coagulation biomarkers ($p \leq 0.05$). Conversely, no correlation between variables was noticed in the control group ($p > 0.05$).

CONCLUSIONS: Aerobic exercise along with a balanced diet modulates sex hormones level, improves homeostasis balance in postmenopausal women, and reduces the potential risk of cardiovascular disease.

Key Words:
Diet, Exercise, Gonadal steroid hormones, Postmenopause, Thrombosis.

Introduction

According to the World Health Organization (WHO), women die primarily from cardiovascular disease (CVD) (23.14%)[1]. In Egypt, CVD is more prevalent in women (8.9%) than men (8.0%) and among those over the age of 50 (11.1%) than those under the age of 50 (5.1%)[2]. Premenopausal women have a 2–6 times lower risk of thrombosis and CVD than postmenopausal women[3]. It can be attributed to the changes in body composition, serum coagulation, fibrinolysis factors, and sex hormones after menopause[4].

Sex hormones influence cardiovascular health in pre-and postmenopausal women. The estradiol hormone has an atheroprotective effect in premenopausal women[3], which includes vasodilation via stimulating endothelial nitric oxide release and prostacyclin[5]. On the other hand, estradiol levels are favorably associated with hypercoagulability, obesity, hyperlipidemia, insulin resistance, and high C-reactive protein in postmenopausal women[3]. This positive relation results in a low-grade inflammation state that transforms from protective to the harmful effect of estradiol after menopause[6].

Moreover, androgens play critical biological roles in premenopausal women, affecting mu-

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scle strength, bone mass, mood, and well-being[7]. However, testosterone increases basal fatty acid uptake and impairs lipolysis in postmenopausal women, causing visceral fat accumulation[8]. Therefore, testosterone is positively associated with lipid accumulation[7] and negatively correlated with high-density lipoprotein cholesterol and sex hormone-binding globulin (SHBG)[9].

Further, increased body fats lead to a higher blood concentration of insulin, subsequently suppressing hepatocyte production of SHBG[8] (a protein produced by the liver, which transports the sex hormones in the blood)[10]. Thereby, lowering the SHBG levels elevates estrogen and androgen levels, inducing hypercoagulability[11], which is recognized by high serum levels of clotting factors and decreased fibrinolysis[12]. Consequently, increased levels of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen in postmenopausal women inhibit fibrinolysis[13], and the reduced Tissue plasminogen activator (tPA) is one of the main characteristics of decreased fibrinolytic activity[14]. Furthermore, shorter prothrombin time (PT) and activated partial thromboplastin time (APTT) are indicators of high coagulation status[15].

Multimorbidity is very common in older adults, as the high consumption of drugs is associated with the possibility of adverse events[16]. Hence, exploring potential non-pharmacological safety interventions that affect sex hormones and improve homeostatic balance is highly demanded.

A healthy lifestyle that includes regular physical activity is accompanied by remarkable health benefits[17] (e.g., lower blood pressure, improved insulin sensitivity, favorable lipid profile, and a significant decline in CVD risk)[18]. The diet is also considered an integral part of lifestyle interventions for decreasing the body mass[17], improving homeostasis balance, and cardiac vascular health in postmenopausal women[19].

Postmenopausal women are highly at risk for CVD, which is connected to hormonal change; thus, we conducted this study to investigate the influence of aerobic exercise and diet on sex hormones and selected coagulation biomarkers after menopause. The hitherto route has not been investigated previously.

Patients and Methods

Study Design and Ethics Approval

According to consort standards, this is a randomized, parallel-controlled study conducted in the outpatient clinics of the Physical Therapy Faculty from 20 September 2020 to 31 May 2021. It was ethically accepted by the Faculty of Physical Therapy, Cairo University, Egypt, before onset (no: P.T.REC/012/002676). All the procedures were according to the Helsinki Declaration for human research conduct. Each woman had been assigned informed consent for participation after a full explanation of the purpose and methods.

Patients

Participants were rounded up from the outpatients of the Department of Internal Medicine, Cairo University Hospital, Egypt, by the study physician (AR), who performed a complete clinical examination for the participants. The eligible 40 postmenopausal women were enrolled according to the inclusion criteria as follows: women in the postmenopausal stage were justified by sex hormones serum levels (i.e., estradiol: 28.04±2.76 pg/ml, free testosterone (FT) level: 1.97±0.50 pg/ml, and total testosterone (TT) level: 0.38±0.077 ng/ml), absenteeism of a menstrual period: 10.45±4.25, age: 65.84±2.95 years, BMI: 37.52±1.28 kg/m^2. The physical activity questionnaire for the elderly was used to assess the level of physical activity[20]. The following criteria were used to exclude participants: smoking, diabetes mellitus, uncontrolled hypertension, any CVD, any pathological disorders that hinder training accomplishment, the involvement in diet programs at the minimum of six months before this study, medications that change blood coagulation, plasma lipids, body weight, or history of hematological disease. Social demographic data were: moderate family income, basic level of education, married, and jobless.

Sample Size, Eligibility, Randomization, and Blinding

The sample size was determined before the study using G*POWER statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany) [t tests-Means: Difference between two independent means (two groups), based on the (Cohen's d) effect size of .73, for outcomes of sex hormones and coagulation factors, α error prob= 0.05, 1-β error prob=0.8 revealed that, the appropriate required sample size for the study was 40.

There were 52 eligible postmenopausal women among the 70 who consented. The reasons for non-eligibility (N=18) include not meeting inclusion criteria (N=8), declining to participate (N=7),

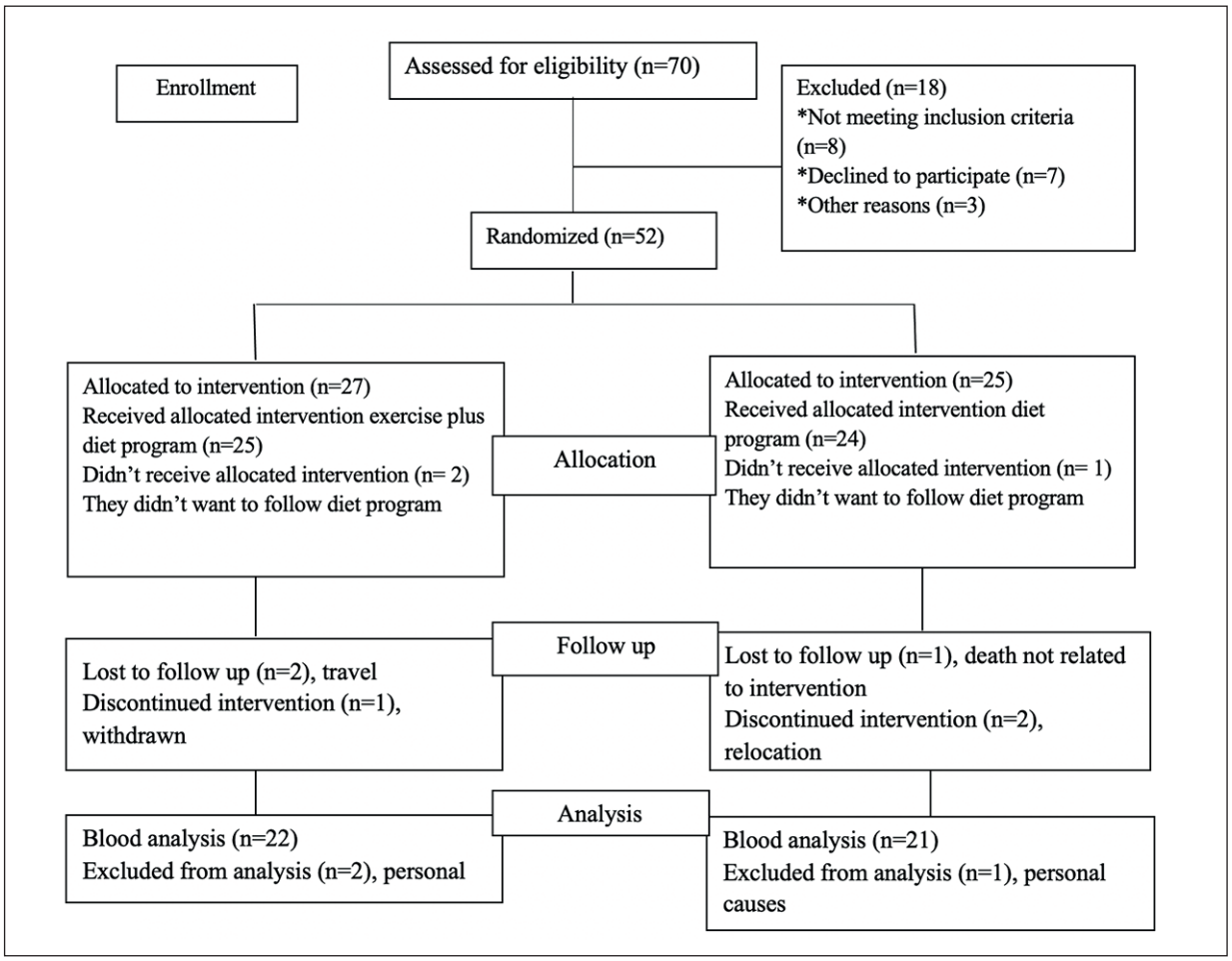

Figure 1. Consort diagram of the present study.

and other reasons (N=3). Fifty-two participants were randomized to treadmill exercise and diet or diet only. Forty out of 52 participants completed the intervention and blood analysis and were only included in statistical analysis (Figure 1).

The block size randomization method was used. Eligible women were randomly set into aerobic exercise and diet restriction (experimental group) or diet restriction only (control group) for 12 weeks (1:1 ratio). A random allocation sequence was generated with Research Randomizer software (Geoffrey C. Urbaniak and Scott Plous, Lancaster, PA, USA), where block sizes were two, four, and six to ensure a balance between two arms concerning the number of participants. Allocations had been hidden in numbered envelopes that were prepared by a staff member who did not participate in this study in a blinded fashion, so the participants and study team members were unaware of the assignment.

Intervention

Exercise protocol for the Experimental Group

The experimental group participants performed continuous moderate-intensity treadmill training (Health Life AC5000 Multi-function Treadmill, China) for alternative days/week during three months, following sports medicine American college guidelines[21]. A physiotherapist and a physician supervised patients during exercise sessions in the study. Participants executed light exercise at the beginning of the training for 10 minutes (warming-up) followed by 30 minutes of treadmill walking at 65%-75% intensity of the maximum heart rate (MHR), as determined by submaximal graded treadmill exercise test using a modified Bruce protocol[22]. Alongside, participants reached 85% of their age-predicted peak heart rate (HR), which is calculated using a va-

lid and reliable formula as HRmax = 220–age[23] and evaluated using POLAR FT1 Monitor. The exercise session ended with 10 minutes of cooling down low-intensity aerobic exercise.

Diet Program

Both groups (experimental and control) followed a personalized balanced calorie-restricted diet described by the dietician following sports medicine American college recommendations[21]. Each participant was limited by a 25% caloric deficit (calculated by Harries Benedict formula)[24]. The balance diet contents were 50–60% carbohydrate, 15–20% protein, and 20–35% fat, with > 25 g of fibers per day coming from vegetables, fruits, and whole grains[25]. Participants were instructed to avoid unhealthy feeding habits and unusual dietary behavior. Diet program adherence by participants was monitored via weekly visits. In addition, study team members introduced and trained participants to use a twenty-four-hour recall and dietary questionnaire of food composition.

Outcomes Measures

Primary Outcomes and Blood Analysis

Venous blood specimens were taken at the start and end of intervention (three months), and the chemiluminescence hormonal analysis was used for all hormones: estradiol, TT, FT, and SHBG. The blood collection occurred between 7:00 and 10:00 AM after fasting for 10 hours. For coagulation factors, plasma was separated with centrifugation of samples at 2000 rpm for 10 minutes at 4°C. PT, APTT, and fibrinogen levels were evaluated by automatic coagulometry (Sysmex CA-1500 System). PAI-1 and tPA values have been measured by enzyme-linked immunosorbent assay (Human PAI1 + tPA ELISA Kit (ab108892). Intra-assay coefficients of variation CV% 5.2%. Inter-assay CV% 10.2%. Sensitivity= 0.06 ng/ml. Range 0.063 ng/ml - 4 ng/ml).

Secondary Outcomes

Anthropometric Measures

Weight (kg) was assessed and divided by the measured square of height (m^2) using the Smart Health Accurate Body Weight Scale (DHM-16/200/300) to calculate BMI.

Statistical Analysis

The results were analyzed by SPSS statistical program version 21.0 (IBM Corp., Armonk, NY, USA). Shapiro–Wilk test was utilized to detect whether the data were normally dispensed. Continuous data were described as mean± standard deviation (SD). Baseline characteristics between both groups were compared by the independent samples *t*-test. Both dependent and independent samples *t*-tests were applied to examine variables before and after the intervention, and differences between experimental and control groups, respectively.

Furthermore, Pearson's correlation coefficient test and stepwise multiple linear regression models were applied to detect the correlation between changes in sex hormones and coagulation factors for each group. *p*-values less than 0.05 were significant.

Results

A total of 40 postmenopausal females were included in the study. All participants were sedentary according to the physical activity questionnaire. There were no statistically significant variances ($p > 0.05$) between the experimental group and the control group in terms of weight, height, age, BMI, sex hormones, or coagulation factors at baseline (**Supplementary Table I**).

According to **Supplementary Table II**, the weight, BMI, serum estradiol, TT, FT, PAI-1, and fibrinogen are significantly reduced. SHBG, tPA, PT, and APTT increased dramatically in the experimental and control groups ($p < 0.01$ and $p < 0.05$, respectively). Besides, the experimental group was significantly higher compared to the control group ($p < 0.01$) after 12 weeks of intervention, as determined by the independent sample *t*-test ($p < 0.01$).

The correlation between variables in the experimental group is illustrated in **Supplementary Table III**; estradiol, TT, and FT are negatively linked with tPA, APTT, and PT, but positively correlated with PAI-1. In contrast, SHBG correlates negatively with PAI-1 and positively with tPA, APTT, and PT ($p \leq 0.05$). However, estradiol and FT reveal a positive correlation with fibrinogen, while TT and SHBG exhibit a negative correlation with fibrinogen ($p \leq 0.05$). In the control group, there was no appreciable correlation between sex hormones and coagulation factors ($p > 0.05$).

According to stepwise multiple linear regression, sex hormones possess no direct effects on coagulation factors in the experimental group ($p > 0.05$), as displayed in **Supplementary Table IV**. Only the change in total testosterone (ng/ml) was found to be a significant predictor of the change in fibrinogen (mg/ml) (B=-8.532 and p =0.030) (**Supplementary Table IV**).

Discussion

Overall, it can be concluded that 12-weeks of aerobic exercise combined with diet led to a statistically significant ($p < 0.01$) decrease in weight, BMI, and serum levels of estradiol, TT, and FT, and an increase in SHBG over restricted balance diet only ($p < 0.05$). These results agreed with Campbell et al[26] and de Roon et al[27], revealing that aerobic exercise and diet inherently reduce estradiol, FT, TT, estrogen, exposure to CVD, and increase SHBG. This change is due to exercise and diet, reducing body weight and fat tissue, which is the principal source of estrogen and androstenedione after menopause[28]. Alongside improving insulin sensitivity and declining insulin level that enhances the hepatic production of SHBG[27], where its increasing promotes lower estrogens and androgens levels[29].

Furthermore, the present study clarified that aerobic exercise with diet restriction significantly ($p < 0.01$) lower coagulation factors (PAI-1, fibrinogen) and increase fibrinolysis markers (tPA, PT, and APTT). Our results are consistent with previous studies[4,30], demonstrating that aerobic exercise and diet regimen enhanced fibrinolytic activity, as PAI-1 exhibited a significant decrease, but PT, APTT, and tPA considerably increased. Various mechanisms can interpret this finding; aerobic exercises enhance the integrity of the vascular endothelium, vascular permeability, and vasodilators release[31], such as nitric oxide that induces the release of tPA from endothelial cells[30] and suppresses PAI-1 production by vascular smooth muscle cells and platelets[32]. Additionally, aerobic exercise increases the serum level of insulin growth factor (IGF)-1, which is a protective factor against the onset and development of atherosclerosis[33]. Further, dietary antioxidants in a balanced diet prevent harmful effects of oxidation on low-density lipoprotein molecules[32] (i.e., abnormalities of endothelium-dependent vasodilation, nitric oxide production suppression, the release of free radicals, and vascular inflammatory cells)[34].

Aerobic exercise and diet restriction decline fibrinogen level through weight loss and FFA decrease[30], which are the essential determinants and stimulators of hepatic fibrinogen production[32]. Consequently, improving thrombolysis action led to prolonging the time of PT and APTT[35].

The present results indicated a significant correlation between sex hormones and coagulation biomarkers that confirmed our hypothesis (i.e., aerobic exercise with diet would induce favorable changes in sex hormones and coagulation biomarkers). Our results corroborate with previous studies[36,37], demonstrating that after menopause, elevated levels of testosterone and estradiol and low SHBG level induce hypercoagulability status, which can be mitigated by the healthy lifestyle that reduces the level of sex hormones[38] and confers desirable benefits on older adult women with a high coagulation profile[39,40].

The current study presented the effect of combined aerobic exercise with a restricted balanced diet on selected coagulation factors and sex hormones. Moreover, the significance of sex hormone fluctuations in promoting hemostatic balance was demonstrated. This kind of intervention is the first one to be applied. In previous studies, the effect of exercise and diet on coagulation factors or sex hormones was presented. Our study revealed that aerobic exercise with diet reduces CVD risk in postmenopausal women, not only by the effect of coagulation biomarkers but also by the change of sex hormones.

Limitations

Nonetheless, our positive outcomes in this study indicate that it is important to consider the current study's limitations; participants' selection was limited to women with no cardiovascular disorders or medical problems. Women with surgical menopause and hormonal therapy were excluded, which may narrow variations in the study results.

Finally, we investigated only one type of exercise and intensity and one diet program; therefore, we cannot generalize results to other exercise types, different intensities, or other diet programs. We recommend further studies about the impact of other kinds of exercises and diet programs on sex hormones and various coagulation factors.

Conclusions

Our study indicated that aerobic exercise combined with a restricted balanced diet changed sex hormones, positively reflecting increased activi-

ty levels of fibrinolytic biomarkers and reduced coagulation factors. We reported the beneficial effects of aerobic exercise with diet on postmenopausal women with a high coagulation profile to illustrate how our approach may permit the delivery of potentially preventative treatment before the physiological consult.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Contribution Statement

M.M and H.F. contributed to data curation, methodology, investigation, conceptualization, A.R and G.E. participated in methodology, editing, supervision, validation, writing-original draft, all authors read and approved the final version of the manuscript, and agreed with the order of presentation of the authors.

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