Effect of acute exercise on postprandial endothelial function in postmenopausal women: a randomized cross-over study

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ABSTRACT

High-sugar intake may cause endothelial dysfunction. It is unknown if a bout of aerobic exercise improves endothelial dysfunction caused by a high-sugar meal in postmenopausal women. This study evaluated if prior aerobic exercise attenuates postprandial endothelial dysfunction in postmenopausal women. Twenty-two postmenopausal women (age [mean±SD]: 60.4±6.5 years; % body fat: 40.3%±7.5%) underwent an exercise (EX) or no exercise (NE) condition, in a random order, 13–16 hours prior to the high-sugar meal consumption. The EX condition included a 60 min bout of supervised aerobic exercise at 75% of age-predicted maximum heart rate. The high-sugar meal, consumed after a 12-hour fast, contained 33% of the subjects' daily energy needs, and 75.6% energy from carbohydrates. Flow-mediated dilation (FMD) and blood concentrations of glucose, insulin, endothelin-1 (ET-1), and nitric oxide (NO) were assessed at baseline and 60 min, 120 min, and 180 min postprandially. Repeated measures analysis test showed that there were no condition by time interaction or condition effects for FMD, glucose, insulin, or NO. There was a significant condition by time interaction but no condition effect for ET-1. Area under the curve was also not different by condition for insulin sensitivity or the above variables. In conclusion, prior aerobic exercise compared with NE did not affect FMD, blood glucose, insulin, ET-1 or NO concentrations, or insulin sensitivity following a high-sugar meal in postmenopausal women. Future studies should look at the effect of different EX intensities on meal-induced endothelial dysfunction in this population.

Trial Registration: ClinicalTrials.gov Identifier: NCT02919488

Significance of this study

What is already known about this subject?

- Endothelial dysfunction, as assessed by flow-mediated dilation, is a risk factor for cardiovascular events. Endothelial function may be impaired during postprandial hyperglycemia.
- Two out of three studies have found that a single bout of exercise may attenuate the impairment of endothelial function following a high-sugar meal.
- None of the above studies were conducted in postmenopausal women, a group that has higher risk for cardiovascular disease than younger individuals. In addition, other markers of endothelial dysfunction such as blood nitric oxide or endothelin-1 were not assessed.

What are the new findings?

- A bout of prior aerobic exercise did not affect postprandial flow-mediated dilation in postmenopausal women.
- A bout of prior aerobic exercise also did not affect other markers of endothelial dysfunction including blood nitric oxide and endothelin-1 concentrations in postmenopausal women.
- In addition, postprandial blood glucose and insulin concentrations and insulin sensitivity were not influenced by a bout of prior aerobic exercise in postmenopausal women.

How might these results change the focus of research or clinical practice?

- Future studies need to evaluate the effect of aerobic exercise of different intensities and resistance training on meal-induced endothelial dysfunction in postmenopausal women.

INTRODUCTION

The endothelium releases substances that affect vasoconstriction (endothelin-1 [ET-1]) and vasodilation (nitric oxide [NO]).[1] A balance between vasoconstriction and vasodilation is needed in order to provide adequate perfusion pressure to target organs.[2] During endothelial dysfunction, this balance is affected leading to impaired vasodilation.[1 2] Endothelial dysfunction, as assessed by flow-mediated dilation (FMD), is a risk factor for cardiovascular events.[3]

Carbohydrate intake can affect endothelial function. According to a meta-analysis, macrovascular endothelial function is impaired during

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postprandial hyperglycemia induced by an oral glucose tolerance test.[4] The impairment has been observed in both healthy subjects and in those with risk factors for cardiovascular disease (CVD).[4] Developing strategies to attenuate postprandial endothelial dysfunction is important given the high intake of added sugars in the US diet.[5] Furthermore, a majority of Americans report consuming several meals and snacks per day possibly impairing FMD for a number of hours.[6]

Exercise (EX) may be a strategy to attenuate the impairment of endothelial function following a high-sugar meal. There are only three studies that have examined the effect of EX on endothelial dysfunction induced by high-sugar intake. Zhu *et al*[7] found that impairment in FMD from an oral glucose tolerance test was restored with a bout of aerobic exercise performed immediately after glucose ingestion in young men. EX also suppressed insulin concentration at 1 hour after glucose ingestion.[7] Weiss *et al*[8] examined the effect of a bout of aerobic exercise performed 17 hours before high-sugar meal consumption in healthy subjects, and found that EX reduced the hyperglycemia-induced impairment in FMD and increased insulin sensitivity. Malin *et al*,[9] on the other hand, reported that an isocaloric bout of high-intensity or moderate-intensity EX had no effect on endothelial function following glucose ingestion in adults with prediabetes. None of these three study measured markers of endothelial dysfunction such as blood NO or ET-1 concentrations and had small sample sizes.[7–9] In addition, the subjects in one of the two studies were all young men,[7] a population that typically does not exhibit a high level of endothelial dysfunction. Whether the same findings apply to older postmenopausal women is unknown. Understanding how prior EX affects high-sugar meal-induced endothelial dysfunction in older women is important given that age is related to endothelial dysfunction[4] and older women have a higher risk for CVD compared with younger women.[10]

The purpose of this study was to determine if postprandial endothelial dysfunction and increases in blood glucose and insulin induced by a high-sugar meal is attenuated with an aerobic exercise bout performed on the previous day in postmenopausal women. Endothelial dysfunction was assessed by FMD, and blood NO and ET-1 concentrations. It was hypothesized that postprandial endothelial dysfunction and increase in glucose and insulin induced by a high-sugar meal would be attenuated by a prior bout of aerobic exercise.

MATERIALS AND METHODS

Participants

Twenty-two postmenopausal women between the ages of 45 years and 75 years were recruited for the study from the Dallas-Fort Worth area. Menopause was defined as not having had a menstrual cycle for at least 1 year. Exclusion criteria included use of medications/supplements to lose weight, following a weight loss diet, smoking, drinking more than seven drinks/week, presence of diabetes, heart disease, stroke, liver, kidney, or untreated thyroid disease, anemia, uncontrolled hypertension, or pulmonary, orthopedic, arthritis or musculoskeletal problems that prevent EX. The study was conducted in the Metabolic and Exercise Physiology laboratories, Department of Kinesiology, Texas Christian University (TCU), from November 2016 to December 2017.

The subjects signed a consent document approved by the TCU Institutional Review Board. The study was conducted according to the Helsinki principles for research with human subjects.

Experimental design

The effect of an acute bout of prior EX compared with no exercise (NE) on postprandial endothelial function was examined, using a randomized cross-over design, with a washout period of ≥7 days. The postprandial endothelial function was assessed in the morning after consumption of a high-sugar meal, and EX or NE was performed 13–16 hours prior to the meal. Randomization was determined by a blocked randomization schema. BAH generated the random allocation sequence, SB and AG enrolled participants, and SB assigned participants to interventions.

EX bout

During the EX trial, the subjects completed a 60-minute bout of supervised aerobic exercise 13–16 hours prior to consumption of the high-sugar meal the following morning. The EX bout comprised of 5 min of warm-up and stretching, 50 min of treadmill walking at 75% of the revised age predicted maximum heart rate,[11] and 5 min of cooldown and stretching. A Polar H7 heart rate monitor was used to monitor heart rate (Polar Electro, Bethpage, New York) and the treadmill speed and incline were adjusted to maintain the target intensity.

High-sugar meal

The high-sugar meal consisted of a cinnamon pastry topped with a sugar glaze and a lemon-lime regular flavored soda. For each subject, the energy content of the meal was 33% of her estimated total daily energy requirement,[12] and contained 75.6% energy from carbohydrate, 21.2% from fat, and 3.2% from protein.

Study protocol

Data on demographics, anthropometry, lifestyle behaviors and health were collected during screening.

Eligible subjects underwent both the EX and NE conditions in a random order. During the EX condition, subjects engaged in a bout of supervised EX for 1 hour 13–16 hours prior to consumption of a high-sugar meal the following morning. The NE condition was similar to the EX condition with the exception that NE was performed. The subjects were asked to fast for at least 12 hours prior to the high-sugar meal consumption. The time when the high-sugar meal was consumed was matched during the two conditions for each subject. The subjects were asked to consume the meal in 20 min and maintain the same meal duration across both conditions. FMD (see description below) was assessed and blood samples were collected in the fasted state before the meal and at 60 min, 120 min, and 180 min from when the meal began. Blood samples were collected through a venous catheter inserted into an antecubital vein on the left arm. The catheter was kept clean and viable by flushing

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with saline solution in between each sample. Blood samples were processed and stored at −80°C until analysis.

Water intake during the postprandial period was standardized (7.1 mL/kg body weight), and 40% was consumed during the first hour and the remaining was consumed in equal proportion during the second and third hours.

The subjects were instructed to refrain from exercising for at least 48 hours prior to each condition. They were also asked to consume the same diet on the day before the high-sugar meal consumption.

Measurements

Demographics, lifestyle behaviors, and health

Data on demographics, lifestyle behavior, and health were collected via questionnaires.

Height, weight, and per cent body fat

Height and weight were measured, using a standard stadiometer (Seca, Chino, California, USA) and digital scale (Seca, Chino, California, USA), and used to calculate body mass index (BMI) (kg/m^2). Per cent body fat was assessed through dual-energy X-ray absorptiometry (Lunar iDXA; GE Healthcare, Chicago, Illinois, USA).

Flow-mediated dilation

All FMD measurements were conducted by a single researcher in a temperature-controlled room. R-wave triggered measurements of the right brachial artery diameter were collected via longitudinal imaging (Acuson Sequoia C512; Mountain View, California, USA) using a 12 MHz linear-array transducer (Acuson 15L8w) placed proximal to the antecubital fossa. Following collection of instantaneous baseline blood flow velocity and 30 s baseline diameter, a standard adult blood pressure cuff wrapped around the subjects' right forearm was inflated to 200 mm Hg to occlude the brachial artery for 5 min.[13] Fifteen seconds after the release of the cuff, instantaneous blood flow velocity was again recorded. Measurement of the artery diameter resumed 30 s after cuff deflation and continued for 3 min. Instantaneous blood flow velocities and vessel diameters were analyzed by a researcher blinded to subject and condition using the semiautomated Brachial Analyzer for Research software (Medical Imaging Applications, Coralville, Iowa). Maximum brachial artery diameter following deflation of the blood pressure cuff and baseline artery diameter were used to calculate FMD expressed as a per cent change from baseline using the following formula: ((maximum diameter – baseline diameter)/baseline diameter)*100. Baseline diameter was defined as the mean diameter of the brachial artery during the 30 s baseline measurement. Maximum diameter was defined as the greatest five-frame-average postdeflation diameter.

Dietary intake and physical activity level

Dietary intake on the day before the high-sugar meal consumption was assessed during both the EX and NE conditions using an image-assisted 24 hours dietary food record. This is a validated method for assessing dietary intake.[14] The subjects were asked to record and take pictures of all the foods and drinks consumed during those days. The images were emailed to the investigators and used to verify the type and amount of foods/drinks recorded by the subjects. The dietary records were analyzed for nutrient content using the Food Processor software program (SQL edition, Salem, Oregon, USA).

Physical activity level was assessed for 48 hours prior to high-sugar meal consumption during both conditions. It was assessed using a 48-hour recall adapted from a validated 7-day physical activity recall.[15]

Blood analysis

The blood samples were analyzed in duplicate for NO and ET-1 using ELISA kits (R&D Systems, Minneapolis, Minnesota, USA). The coefficients of variation for NO and ET-1 were 8.0% and 3.9%, respectively.

Glucose and insulin were assessed from serum samples by SpectraCell Laboratories (Houston, Texas, USA) which is both Clinical Laboratory Improvement Amendments and New York State certified. The laboratory assessed glucose using the Beckman Coulter procedure[16] and insulin by immunoturbidimetric assay.[17]

Sample size calculation and statistical analysis

A sample size of 20 subjects was estimated based on a mean difference of 2.5% in FMD between the EX and NE conditions and SD of 3.0%.[7] This sample size would provide a power of 0.96 at $\alpha=0.05$ for the overall model, and a power of 0.82 at $\alpha=0.0125$ for multiple comparisons (four time points). The sample size in the present study was higher (n=22) than the estimated sample size (n=20).

Baseline variables including FMD, NO, ET-1, insulin, glucose, and body weight were compared by condition using a paired t-test. Data on insulin and NO were log transformed before being analyzed. Energy intake on the day before the high-sugar meal consumption and EX duration over the past 48 hours prior to meal consumption were compared between conditions using the Wilcoxon signed-rank test.

A mixed-effects model repeated-measures analysis was used to evaluate the effect of time (baseline and 60 min, 120 min, 180 min after the initiation of the meal) and condition (EX or NE), and the interaction between time and condition on FMD (per cent change of the vessel diameter), ET-1, NO, glucose, and insulin. Differences ($p<0.05$) in these variables by condition and time were further assessed by least square mean contrasts. NO and insulin were not normally distributed and were log transformed before being analyzed. One FMD value, for a single subject, at 120 min during the EX condition, was excluded from the analysis because the subject moved during the procedure making it difficult to analyze the artery diameter. The data on normally distributed variables (FMD, ET-1, and glucose) are presented in the figures as arithmetic means and 95% CIs whereas the data on variables that were not normally distributed (NO and insulin) were presented as geometric means and 95% CIs.

Area under the curve (AUC) was computed for FMD, NO, ET-1, insulin and glucose, and insulin sensitivity using the trapezoidal rule. Insulin sensitivity was calculated using the Matsuda and DeFronzo Insulin Sensitivity Index.[18] AUC was compared between conditions by paired t-test. NO and insulin AUC were log transformed prior to analysis. The

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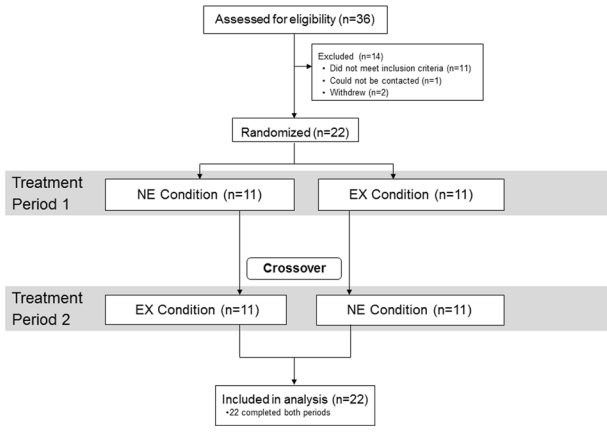

Figure 1 Consort diagram. The number of subjects assessed for eligibility, excluded, randomized, completed the study, and included in the statistical analysis. EX, exercise; NE, no exercise.

AUC data are shown as medians, 25th and 75th centiles, and 10th and 90th centiles in the figures.

Meal sequence effect was assessed by including the meal sequence as a factor in the mixed-effects models and interpretation of results were unchanged.

SAS statistical package V.9.4 (SAS Institute, Cary, North Carolina, USA) was used for analysis. A two-sided p value <0.05 was considered statistically significant.

RESULTS

Flow chart

The study consort diagram is presented in figure 1. Thirty-six individuals were screened for eligibility. Of these, 11 women were excluded from the study (one subject was a breast cancer survivor and the blood pressure cuff caused swelling in her arm, one took aspirin, one had heart disease, one was a smoker, one had anemia, one did not meet the age criteria, one had autoimmune/inflammatory condition, and four were not postmenopausal), one woman could not be reached, and two dropped out (one due to a car wreck and one due to a sick family member). Twenty-two subjects were included in the study and completed it. Eleven subjects were randomly assigned to the EX condition first. These subjects completed the EX condition first followed by the NE condition. Eleven subjects were randomly assigned to the NE condition first. These subjects completed the NE condition followed by the EX condition. Data during both conditions were obtained on 22 women.

Subject characteristics

All subjects were white women and 77.3% were non-Hispanic. Mean±SD for age was 60.4±6.5 years. Mean BMI, % body fat, and waist circumference were 26.8±6.3 kg/m^2, 40.3±7.5%, and 92.5±13.4 cm, respectively. Five subjects were taking medications for hypertension and four for dyslipidemia. There was no change in the type and dose of these medications during the two conditions. In addition, adjusting for the use of these medications/supplements did not have an effect on the outcome variables.

Table 1 Baseline data on flow-mediated dilation, nitric oxide, endothelin-1, glucose, insulin, and body weight, and energy intake over past 24 hours and exercise duration over past 48 hours by condition

Variable	NE condition (n=22)	EX condition (n=22)	P value*
Flow-mediated dilation (%)	8.4±3.5	9.0±4.3	0.99
Nitric oxide (µmol/L)	23.6 (16.7, 43.4)	21.9 (17.0, 34.0)	0.85
Endothelin-1 (pg/mL)	1.7±0.4	1.6±0.5	0.25
Glucose (mg/dL)	94.3±11.5	93.4±10.0	0.49
Insulin (µIU/mL)	8.3 (6.5, 10.8)	7.8 (5.7, 10.2)	0.30
Body weight (kg)	71.3±17.5	71.2±16.8	0.76
Energy intake over past 24 hours (kcal)	1503 (1182, 2473)	1499 (1234, 2521)	0.53
Exercise duration over past 48 hours (min)	0 (0, 0)	0 (0, 0)	1.0

Data on nitric oxide, insulin, energy intake over the past 24 hours, and exercise duration over the past 48 hours are shown as medians and 25th and 75th centiles, and data on the remaining variables are shown as means and SD.
*P values indicate differences by meal condition and were determined by paired t-test for flow-mediated dilation, nitric oxide, endothelin-1, glucose, insulin, and body weight, and by Wilcoxon signed-rank test for energy intake over the past 24 hours and exercise duration over past 48 hours. The data on nitric oxide and insulin were log transformed before analysis.
EX, exercise; NE, no exercise.

Baseline variables

Baseline variables are shown in table 1 and include fasting FMD and NO, ET-1, glucose, and insulin concentrations, and body weight by condition. It also includes energy intake (during the 24 hours prior to high-sugar meal consumption) and EX duration (during the 48 hours prior to high-sugar meal consumption) by condition. None of the above variables were different by condition.

Glycemic response

The data on glucose, insulin, and insulin sensitivity are shown in figure 2.

Glucose

A significant time effect was found for glucose (p<0.0001). There were no condition (p=0.75) or condition by time interaction (p=0.79) effects on glucose, however. Glucose response (arithmetic mean [95% CI]) in the NE condition was significantly (p<0.05) elevated at 60 min compared with the baseline value (baseline: 94 [89, 99] mg/dL; 60 min: 120 [105, 134] mg/dL, respectively). Glucose response in the EX condition was significantly (p<0.05) elevated at 60 min and lower at 180 min compared with the baseline value (baseline: 93 [89, 98] mg/dL; 60 min: 121 [105-138] mg/dL; 180 min: 80 [75-86] mg/dL, respectively). There was no difference by condition in the AUC values for glucose (p=0.93).

Insulin

There were no condition (p=0.45) or condition by time interaction (p=0.36) effects on insulin. A significant time effect on insulin was observed (p<0.0001). Insulin (geometric means [95% CI]) was significantly (p<0.05) elevated at 60 min and 120 min compared with the respective baseline values within each condition (NE: baseline:

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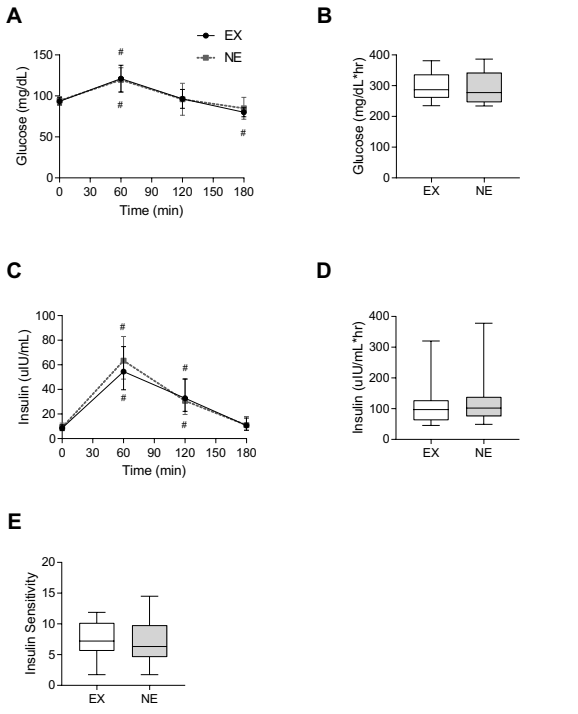

Figure 2 Effect of a prior bout of aerobic exercise versus no exercise on postprandial glucose, insulin, and insulin sensitivity responses in 22 postmenopausal women. The line graphs show glucose (A) as arithmetic means and 95% CIs and insulin (C) as geometric means and 95% CI. The box plots show area under the curve (AUC) for glucose (B), insulin (D), and insulin sensitivity (E). The line within the box is median, the lower and upper limits of the box are 25th and 75th centiles, and the error bars are 10th and 90th centiles. Insulin was log transformed before being analyzed. A mixed-effects model repeated-measures analysis showed a significant time effect ($p<0.0001$) but no condition or condition by time interaction effect for glucose or insulin. AUC for glucose, insulin, and insulin sensitivity were not different by conditions. Compared with time 0 within each condition: #$p<0.05$. EX, exercise; NE, no exercise.

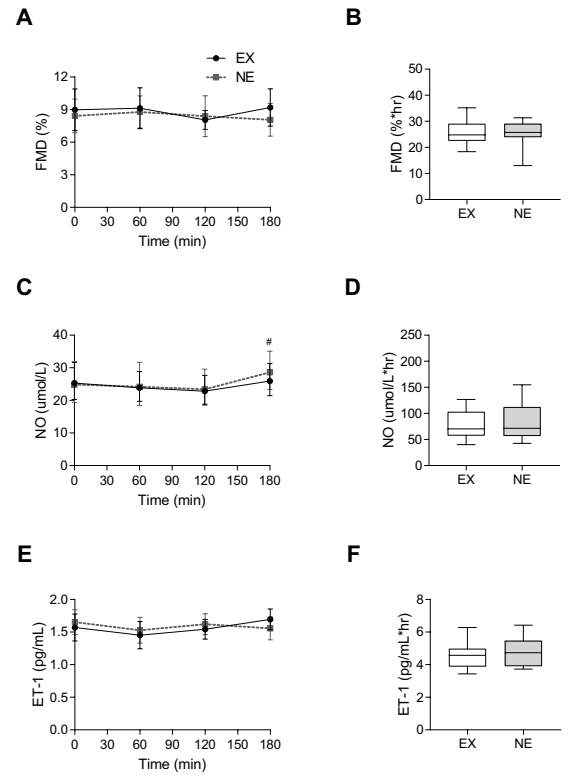

Figure 3 Effect of a prior bout of aerobic exercise versus no exercise on flow-mediated dilation (FMD) , nitric oxide (NO), and endothelin-1 (ET-1) responses in 22 postmenopausal women. The line graphs show FMD (A) and ET-1 (E) as arithmetic means and 95% CIs and NO (C) as geometric means and 95% CI. The box plots show area under the curve (AUC) for FMD (B), NO (D), and ET-1 (F). The line within the box is median, the lower and upper limits of the box are 25th and 75th centiles, and the error bars are 10th and 90th centiles. NO was log transformed before being analyzed. There were no time, condition, or condition by time interaction effects on FMD. There were no condition or condition by time interaction effects but a significant time effect ($p=0.008$) on NO. A significant condition by time interaction effect ($p=0.03$) was observed for ET-1 but post hoc analysis found no differences between conditions or within conditions. AUC for FMD, NO, and ET-1 were not different by conditions. Compared with time 0 within each condition: #$p<0.05$. EX, exercise; NE, no exercise.

9.1 [6.6, 12.6] µIU/mL; 60 min: 63.4 [48.4–83.1] µIU/mL; 120 min: 30.8 [19.7, 48.2] µIU/mL, respectively; EX: baseline: 8.6 [6.6, 11.3] µIU/mL; 60 min: 54.5 [39.7, 74.8] µIU/mL; 120 min: 32.8 [22.1, 48.6] µIU/mL, respectively). AUC for insulin was not different between the two conditions ($p=0.18$).

Insulin sensitivity

There was no difference in AUC for insulin sensitivity by condition ($p=0.86$).

Endothelial function

The data on FMD, NO, and ET-1 are shown in figure 3.

Flow-mediated dilation

There were no time ($p=0.82$), condition ($p=0.48$), or condition by time interaction ($p=0.69$) effects on FMD. The AUC for FMD was also not different by condition ($p=0.55$).

Nitric oxide

There were no condition ($p=0.71$) or condition by time interaction effects on NO ($p=0.44$). The time effect was significant, however ($p=0.008$). NO (geometric mean [95% CI]) was significantly elevated ($p<0.05$) at 180 min compared with the baseline value in the NE condition (baseline: 24.9 [19.4, 31.9] µmol/L; 180 min: 28.6 [23.4, 35.1] µmol/L, respectively). There was no difference in AUC for NO by condition ($p=0.68$).

Endothelin-1

A significant condition by time interaction effect ($p=0.03$) was observed for ET-1 indicating a differential response between conditions. However, post hoc analysis did not show any differences between conditions at the different

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time points or between the baseline and other time points within condition. AUC for ET-1 was not different by condition (p=0.31).

DISCUSSION

This was the first study to evaluate the effect of a prior bout of aerobic exercise on high-sugar meal-induced endothelial dysfunction in postmenopausal women. As expected, the high-sugar meal elevated glucose and insulin concentrations during the postprandial period but there were no differences between the EX and NE conditions. There were also no differences in FMD and ET-1 concentrations over time or by condition, and NO concentration was not different by condition.

Postprandial glucose concentration was higher at 1 hour and insulin concentration at 1 hour and 2 hours compared with baseline in both the NE and EX conditions. There were no differences in fasting or postprandial glucose and insulin responses or insulin sensitivity between the two conditions. Zhu *et al*[7] found no differences in fasting or postprandial glucose responses between an EX and NE condition in healthy young men who underwent an acute bout of aerobic exercise or NE, in a random order, immediately following an oral glucose tolerance test. Postprandial insulin response was lower at 1 hour in the EX compared with the NE condition, however.[7] Weiss *et al*[8] implemented an acute bout of aerobic exercise or NE, in a random order, 17 hours prior to high-sugar meal consumption in healthy subjects, and reported a downward shift in postprandial glucose and insulin responses but no differences in fasting responses during the EX compared with the NE trials. Malin *et al*[9] evaluated the effect of a single bout of high intensity EX or low intensity EX, or NE, administered in a random order, prior to an oral glucose tolerance test in subjects with prediabetes, and found a lower glucose response at 2 hours after the oral glucose tolerance test (OGTT) during the EX trials compared with the control trial. A reason why EX did not affect postprandial glucose or insulin responses in our study may be related to age. The subjects in our study were much older than the subjects in the other three studies, and this may affect the ability to attenuate postprandial glucose response with EX. Tsintzas *et al*[19] examined how age affects glucose and insulin responses to a single bout of resistance EX and found that older men compared with younger men exhibited higher glucose responses at baseline and over 48 hours but no difference in insulin responses.

FMD did not change during the postprandial period compared with the respective baseline value within each condition, and there was no significant difference by condition. Malin *et al*[9] also reported that a prior bout of high or moderate-intensity EX compared with NE did not affect FMD post-EX or during an oral glucose tolerance test. Zhu *et al*,[7] however, reported that postprandial FMD was suppressed in the NE condition at 1 hour but did not change in the EX condition compared with the respective baseline value. Weiss *et al*[8] reported a higher FMD at baseline and during the postprandial period in the EX compared with the NE condition. The carbohydrate content of the meal in the present study could not explain why FMD was not suppressed during the postprandial period in the NE condition since our study contained more carbohydrate than the amount administered by the other three studies.[7–9] The lack of effect of EX on FMD in the present study may not be explained by the presence of atherosclerosis, known to affect vasodilation, since we excluded subjects with coronary heart disease. In addition, adjusting for use of medications for dyslipidemia did not change the outcomes. The studies[7 8] that did find a higher postprandial FMD in the EX condition had younger subjects compared with the subjects in the present study. Malin *et al*,[9] who did not find any effect of EX on postprandial FMD had older subjects than those in the studies by Zhu *et al*[7] and Weiss *et al*.[8] Older age is associated with more arterial stiffness than younger age.[20] Kitzman *et al*[21] found no improvement in FMD or arterial stiffness with endurance EX in an older group of mostly female patients with heart failure (with preserved ejection fraction). Pierce *et al*[22] reported that EX training did not improve FMD in postmenopausal women but increased it in middle age and older men compared with controls. Another possible reason for no change in postprandial FMD due to EX in our study may be related weight status. The subjects in the studies by Zhu *et al*[7] and Weiss *et al*[8] were leaner than those in our study and that by Malin *et al*.[9] Hallmark *et al*[23] have reported that FMD response to acute EX is blunted in obese compared with lean subjects. Estrogen replacement therapy (ERT) has been found to improve FMD in estrogen-deficient postmenopausal women.[24] Two out of 22 women in the present study took ERT at the same dose throughout the study. Adjusting the analysis for ERT use did not change the results.

NO at baseline or during the postprandial period was not different between the EX and NE conditions. It was, however, higher at 180 min compared with the respective baseline concentration in the NE condition. Neither Zhu *et al*,[7] Weiss *et al*,[8] nor Malin *et al*[9] assessed NO. The results in the present study are unexpected since acute hyperglycemia has been found to suppress NO in healthy adults in vivo[25] and acute EX has been found to increase NO in healthy subjects.[26] The subjects in these studies were mostly young adults.[25 26] The older age of the participants in the present study may have influenced their NO response. Tessari *et al*[27] have shown that whole body NO production is lower in older compared with younger controls. However, according to the study by Nyberg *et al*[28] lifelong physical activity prevents the age-associated reduction in arterial NO bioavailability in older adults.

ET-1 was not reduced after the meal in the EX compared with the NE conditions. Caballero *et al*[29] have reported that ET-1 is higher in subjects with type 2 diabetes compared with normoglycemic controls. Maeda *et al*[30 31] have found that aerobic exercise training decreased ET-1 in healthy middle-aged and older women. More recently, Nyberg *et al*[32] have shown that aerobic exercise training opposed the age-related increase in ET-1 in older subjects and normalized ET-1 in middle-aged subjects with hypertension. The studies by Zhu *et al*,[7] Weiss *et al*,[8] and Malin *et al*[9] did not assess ET-1.

A limitation of the present study was that EX intensity was not determined using aerobic submaximal or maximal assessment. Because our postprandial period was limited to 3 hours, it is possible that we missed some of the postprandial responses beyond that period. Our results can only be applied to postmenopausal women. A strength of the

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study was that the meal size was based on the subjects' estimated resting metabolic rate. The sample size in the present was higher than that estimated based on the sample size calculation. The study was a randomized controlled study. Lastly, the study assessed markers of endothelial dysfunction including ET-1, and NO. Other markers of endothelial dysfunction such as angiotensin II, plasminogen activator inhibitor-1, and Von Willebrand factor were not assessed, however.

Future studies in postmenopausal women should include other markers of endothelial dysfunction besides ET-1 and NO and have a longer postprandial period. The studies should also evaluate the effect of aerobic exercise of different intensities and resistance training on meal-induced endothelial dysfunction in this group.

In conclusion, prior aerobic exercise compared with NE did not affect FMD, blood glucose, insulin, ET-1 or NO concentrations, or insulin sensitivity following a high-sugar meal in postmenopausal women.

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