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Predictors of Endothelial Function in Employees with Sedentary Occupations in a Worksite Exercise Program

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Abstract

A sedentary work force may be at increased risk of future cardiovascular disease. Exercise at the worksite has been advocated, but effects on endothelium as a biomarker of risk and relation to weight loss, lipid changes or circulating endothelial progenitor cells (EPCs) have not been reported. Seventy-two office and laboratory (26 with body-mass index [BMI] > 30 kg/m^2) employees (58 women; average age 45 years; range: 22-62 years) completed 3 months of participation in the National Heart, Lung, and Blood Institute's "*Keep the Beat*" program, with determination of vital signs, laboratory data and peak oxygen consumption (VO_2) during treadmill exercise. Brachial artery endothelium was tested by flow-mediated dilation (FMD), which at baseline was inversely associated with Framingham risk score (r=-0.3689, P<0.0001). EPCs were quantified by colony assay. With exercise averaging 98±47 (mean±SD) minutes each work week, there was improvement in FMD (from 7.8 ±3.4 to 8.5±3.0%, P=0.0096) and peak VO_2 (+1.2±3.1 mL O_2/kg/min; P=0.0028), with reduction in diastolic blood pressure (-2±8 mmHg; P=0.0478), total cholesterol (-8±25 mg/dL, P=0.0131), low-density lipoprotein (LDL) cholesterol (-7±19 mg/dL, P=0.0044), but with marginal reduction in weight (-0.5±2.1 kg, P=0.0565). By multiple regression modeling, lower baseline FMD, greater age, reductions in total and LDL cholesterol and diastolic blood pressure, and increases in EPC colonies and peak VO_2 were jointly statistically significant predictors of change in FMD and accounted for 47% of the variability in FMD improvement with program participation. Results were similar when modeling was performed for women only. By contrast, neither adiposity at baseline nor change in weight were predictors of improved endothelial function. In conclusion, daily exercise achievable in the worksite by employees with sedentary occupations improves endothelial function—even with absence of weight loss--which may decrease cardiovascular risk, if sustained.

Keywords

endothelium; nitric oxide; obesity; lipoproteins; exercise

Exercise has been associated with multiple health benefits, including favorable effects on lipids, blood pressure, insulin sensitivity and endothelial function[1-5], yet almost two-thirds of

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American adults do not engage in any form of routine exercise[6], suggesting that many individuals find the time commitment recommended by these organizations challenging or impractical, possibly because of demands of work and family. We utilized the National Heart, Lung, and Blood Institute's comprehensive workplace health intervention—called *Keep the Beat*—which includes worksite exercise facilities, to determine predictors of an important marker of cardiovascular risk (endothelial nitric oxide bioactivity[7,8]) and whether individuals with sedentary occupations could improve endothelial function with relatively brief periods of daily exercise achievable during the work week.

Methods

This study was conducted at the Clinical Center of the National Institutes of Health with employees enrolled in the *Keep the Beat* wellness program. All subjects provided informed consent to participate in this protocol, approved by the institutional review board of the National Heart, Lung, and Blood Institute. Female participants were non-pregnant, and all subjects had no known coronary artery or other vascular disease and reported no regular daily exercise activity. No medications or hormone therapies had been initiated within one month of enrollment. All subjects underwent a focused cardiovascular physical examination, and venous blood samples were drawn in the fasting state for routine chemistries and blood counts, lipid profile, glucose, insulin, estradiol and follicle-stimulating hormone for women, C-reactive protein (hsCRP) and assays for EPCs derived from mononuclear cells isolated from blood sample. Insulin sensitivity was estimated from fasting glucose and insulin values using the Homeostasis Model Assessment.[9] Cardiovascular risk scores were calculated using the Framingham Heart Study Prediction Score Sheet for men and for women (www.nhlbi.nih.gov/about/framingham/riskabs.htm). Study participants underwent brachial artery reactivity testing to assess endothelial function and metabolic treadmill stress testing to assess level of fitness.

After baseline data were obtained, all subjects received a *Keep the Beat* binder which provided subjects with 15 minute exercise programs for the fitness centers equipped with endurance training (stationary bicycles, elliptical trainers) and muscle-strengthening devices, and information about additional exercise during the workday (stairs at work, walking maps for NIH campus). Study participants were requested to record total exercise time per week on diary sheets. At the end of 3 months, subjects returned to the Clinical Center for repeat of all testing performed at baseline, between 48 and 72 hours after the last exercise session. All subjects continued on their current medications throughout the study as prescribed by their health care providers, without change in dosages or initiation of new medications. Participants were in contact with the protocol coordinator on a weekly basis, with submission of exercise diaries.

Brachial artery flow-mediated dilation (FMD) as an index of endothelial function was performed by a single experienced technician, who also performed this testing in a study reported previously from our center.[10] Imaging of the left brachial artery proximal to the antecubital fossa was performed using a high-resolution ultrasound (12.5 MHz linear-array transducer) following 10 minutes of rest. FMD was determined as the maximum increase in diameter of the brachial artery during reactive hyperemia created by an inflated cuff (200 mmHg for 5 minutes) on the forearm, distal to the measurement site. Arterial diameter was measured in millimeters from the leading edge of the intima-lumen interface of the near wall (echo zone three) to the leading edge of the lumen-intima interface of the far wall (echo zone five), coincident with the R-wave on the electrocardiogram (i.e., end-diastole). FMD was calculated as: % vasodilation = ([post-ischemia - baseline diameter] × 100)/ baseline diameter. The intra-observer variability of this analysis (measured twice in blinded fashion by a single operator) was assessed in 15 subjects by this technician, with a correlation coefficient of 0.885.

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Symptom-limited cardiopulmonary treadmill exercise testing was performed using the standard Bruce protocol. Respiratory gas analysis was performed using a breath-by-breath analysis of O_2 and CO_2 on a SensorMedics VMAX 229c instrument (Yorba Linda, CA). Peak oxygen consumption relative to body weight (peak VO_2) as a measure of exercise fitness, peak respiratory exchange ratio (VCO_2/VO_2) as a measure of exercise effort and the ventilatory response to peak exercise (VE/VCO_2) were expressed as the highest 20 second averaged samples during the last stage of the exercise test. Anaerobic threshold was determined by the ventilatory equivalents method.[11]

Blood was collected into tubes with Ficoll and sodium heparin for isolation of mononuclear cells, washed twice in phosphate-buffered saline with 5% fetal bovine serum and re-suspended in media (Stem Cell Technologies EndoCult Basal Media with Supplements, Vancouver, BC, Canada) for endothelial progenitor colony-forming assay. Cells were plated on dishes coated with human fibronectin (BIOCOAT® Becton Dickinson Labware, Bedford, MA) at a density of 5×10^6 cells per well and incubated at 37 °C in humidified 5% CO_2. After 48 hours, the non-adherent cells suspended in the growth media were re-plated onto fibronectin-coated 24-well plates at a density of 10^6 cells per well. After 5 days, colony-forming units, defined as a central core of rounded cells surrounded by elongated and spindle-shaped cells, were counted manually in 4 to 8 wells of a 24-well plate. Interobserver variability of colony determination was assessed by 2 investigators who independently counted colonies in wells from 7 participants; agreement was excellent, with correlation coefficient of 0.998.

Flow cytometric analysis was used to quantify potential endothelial progenitor cells (CD133/VEGFR-2) using fluorochrome-conjugated antibodies [Miltenyi Biotec (Auburn, CA) CD133 APC; R&D Systems (Minneapolis, MN) VEGFR-2 PE]. Lymphocytes of B and T lineages were excluded from analysis using fluorochrome-conjugated antibodies with appropriate isotype controls [BD Biosciences (San Jose, CA) CD3, CD19, CD33 FITC]. All cells were stained with either 7AAD (BD Biosciences) or Live/Dead (BD Biosciences) to allow exclusion of dead cells. A subset of samples was stained with Hoescht (Invitrogen, Carlsbad, CA) to ensure the flow cytometer was counting nucleated cells (<1% of cells were non-nucleated). The Cyan flow cytometer was used with Summit Software (Dako, Ft Collins, CO) for data acquisition and FCSExpress (De Novo Software, Thornhill, ONT, Canada) for analysis.

Laboratory, exercise fitness and brachial artery endothelial testing were performed and interpreted by separate investigators without knowledge of one another's findings. Data are reported as mean value ± standard deviation, unless otherwise indicated. As prespecified in the protocol, FMD of the brachial artery--a bioassay for endothelial nitric oxide bioactivity--was chosen as the primary measure of vascular health in our cohort of sedentary individuals. The study was designed to detect a 1% absolute improvement in FMD based on a sample size of 88 subjects ($\beta= 0.80$, $\alpha= 0.05$). Covariates of interest as predictors of change in FMD were age, baseline FMD, and baseline and 3-month changes in exercise fitness (peak VO_2), BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin, fasting glucose, hsCRP, and EPC colony-forming units. The covariates were first investigated as univariate predictors of change in brachial artery FMD using simple linear regression and correlation analysis. Multiple regression models for explaining changes in FMD during program participation were then constructed using the forward, backward, and stepwise model-building approaches. Covariates found significant in the stepwise model with Type II sums of squares were re-run using the general linear model with Type III sums of squares. Therefore, the p-value for each covariate reflects adjustment for all other model covariates. The models were rerun on the *a priori* specified subgroup of women only. All analyses were performed using the SAS statistical analysis package, utilizing the STEPWISE, GLM, and MEANS procedures (SAS User's Guide: Statistics, Version 9 Edition: SAS Institute Inc, Cary, NC). All reported p-values are based on two-sided *t*-tests for

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continuous data (hsCRP data were log-transformed) or Fisher's Exact Test for comparison of proportions.

Results

Characteristics of the 72 study participants are shown in Table 1. BMI was directly associated with Framingham risk score (r=0.2263, P=0.0180) and inversely associated with exercise fitness (r=-0.6425, P<0.0001). Participants averaged 98±47 minutes of exercise each work week, and showed statistically significant improvements in level of exercise fitness (peak VO_2) and exercise duration on the standard Bruce protocol (Table 2). Improvement in level of fitness was inversely associated with age (r=-0.3283, P=0.0075), but was not related to level of fitness at baseline (r=-0.1031, P=0.4137), BMI at baseline (r=-0.1868, P=0.1368) or weight loss during program participation (r=-0.1761, P=0.1745). Study participants also experienced statistically significant reduction in diastolic blood pressure, total cholesterol and LDL cholesterol, with similar improvement for men and for women (all P>0.1999 for comparisons). Reduction in diastolic blood pressure and total cholesterol was inversely related to baseline values (r=-0.4806, P<0.0001 and r=-0.2860, P=0.0149, respectively), with trend towards similar relationship between baseline values and reduction in LDL cholesterol levels (r=-0.2199, P=0.0635). HDL cholesterol levels declined slightly, but significantly for the cohort, with greater decline in men than women (-6±8 versus -1±8 mg/dL, P=0.03). Weight loss was minimal for the cohort (-0.5±2.1 kg; P=0.0565), and similar for men and women (P=0.4230), but proportionate to the length of time devoted to exercise on a weekly basis (r=-0.3425, P=0.0042). Insulin sensitivity did not change for the cohort as a whole, although it tended to improve proportionate to weight loss (r=0.221, P=0.0511). Changes in blood pressure and lipoprotein values were not associated with baseline BMI or change in weight during the program (all P> 0.50). Nineteen subjects took medications for hypertension or hypercholesterolemia, or were on hormone therapies for contraception or menopause. Trend towards reduction in systolic blood pressure (-3±13 mmHg, P=0.066) was noted in this group: otherwise, changes in diastolic blood pressure and lipid values were no different for these 19 participants than changes in the 53 subjects not on these treatments (all P> 0.40).

At baseline, FMD was inversely associated with Framingham risk score (r=-0.3689, P<0.0001). FMD improved significantly for study participants (Table 2), and was similar for the 19 subjects on medications versus the 53 subjects not on medications (P=0.9185). Participants also showed increases in numbers of EPC colonies (from 37±47 to 54±55 colonies per well, P=0.0003) and, in the subset who underwent this measure, increases in CD133+/ VEGFR2+ cells by flow cytometry, from 3±4 to 19±3 cells/mL blood (P=0.0001).

Because of the association between endothelial function and cardiovascular risk reported in previous studies[7,8], change in FMD following 3 month program participation was prespecified as the primary endpoint in our study. No statistically significant univariate predictors of change in FMD were found over the range of covariates examined. By multiple stepwise procedure, lower baseline FMD, reduction in total cholesterol, reduction in LDL cholesterol, reduction in diastolic blood pressure, greater age, and increase in EPC colonies were jointly significant predictors at the $P \leq 0.05$ level, with improvement in peak oxygen consumption during exercise of borderline significance (Table 3). The combination of these covariates in this model provides a cumulative coefficient of determination (model R^2) of 0.4676, indicating that almost half of the variation in improvement in FMD as a result of program participation was accounted for by these covariates. The results remained essentially unchanged when the models were rerun separately on the subset of 58 women, representing 81% of study finishers. By contrast, neither adiposity at baseline nor change in weight during program participation were predictors of improved endothelial function.

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Discussion

The most recently revised diet and lifestyle recommendations from the American Heart Association encourage a balance of caloric intake and physical activity to achieve and maintain a healthy body weight (18.5 to 24.9 kg/m^2).[12] Reports that the majority of Americans do not exercise regularly, coupled with the increasing prevalence of obesity, indicate that many find these recommendations impractical or challenging, possibly because of time demands of work and family responsibilities. We determined that level of fitness and brachial artery endothelial function were inversely associated with Framingham risk score in our cohort of largely overweight or obese employees with sedentary occupations. We found that 15-20 minutes of exercise daily, using facilities provided at the worksite, can improve endothelial function in a relatively brief period of 3 months. Although obesity at baseline was associated with diminished exercise fitness and higher Framingham risk score, benefits of program participation to exercise fitness, lipids, blood pressure and endothelial function were independent of body mass at baseline as well as weight loss during program participation, which was minimal for the entire group. In general, weight loss was achieved by those participants who devoted more time to exercise, with weekend activity in addition to exercise during the work week which, in turn, was weakly associated with improved insulin sensitivity.

Other groups have examined the health benefits of worksite physical activity programs, with reviews of such programs reporting limited or inconclusive benefits.[13-16] Improvement in exercise fitness, blood pressure, and total and LDL cholesterol observed in our cohort not seen in other studies may be due to a more overweight or obese cohort in our study and provision of exercise facilities with endurance and muscle-strengthening equipment at 3 locations to facilitate easy access to employees. Of interest, improvement in these parameters was seen both in subjects on medications or hormone therapies (treatments for at least one month prior to enrollment with no changes during participation in the study) as well as in the larger cohort on no medications that could affect study endpoints.

Our study provides insight into the potential health benefits of worksite exercise with respect to endothelial function, a biomarker of cardiovascular risk.[7,8] Improvement in endothelial function as a result of exercise training may result from repetitive shear stress effects on endothelium, with increased transcription or phosphorylation of the primary enzyme for nitric oxide synthesis, endothelial nitric oxide synthase.[17] In our cohort, significant improvements in exercise duration and brachial artery reactivity were determined after 3 months of program participation. By multiple regression modeling, lower baseline FMD, greater age, reductions in total and LDL cholesterol, reduction in diastolic blood pressure, increases in EPC colonies and improvement in exercise fitness accounted for nearly half of the variability in improved brachial artery flow-mediated dilation with program participation, suggesting multifactorial contribution to improvement in endothelial function. By contrast, neither BMI at baseline nor change in weight during program participation was a predictor of improved endothelial function.

An mechanism proposed previously for improvement in endothelial function is that exercise may mobilize bone marrow-derived EPCs into the circulation, with attachment to arteries in the circulation and replacement of dysfunctional endothelium.[18-20] We demonstrated increases in number of EPCs measured by colony assay and, in a subset, by flow cytometry. By multiple stepwise procedure, the increase in EPC colonies made a small but statistically significant contribution to improvement in endothelial function in our study participants.

An unanticipated finding in our study was that HDL cholesterol levels actually declined during program participation, especially in men. Previous studies have shown that exercise may increase HDL cholesterol levels, but a recent meta-analysis of 25 randomized clinical trials

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concluded that likely there may be critical determinants for significant increase in HDL cholesterol, including minimum exercise volume (>120 minutes of weekly exercise).[21] Longer durations of daily exercise may also be required for weight loss (which was minimal in our cohort), improvement in insulin sensitivity and reduction in levels of CRP. Reduction in hsCRP was reported for 199 healthy women participating in a 2-month exercise program in which average weight loss was 3 kg.[22]

Limitations of our study include the non-randomized design, although testing was performed by different investigators without knowledge of one another's results. Exercise time per week was self-reported and not all subjects used the exercise equipment provided in the rooms for the same duration of time or intensity of exercise. Nonetheless, participants showed significant improvement in exercise fitness, both by increased duration of exercise during treadmill stress testing and measurement of peak oxygen consumption. Reproductive-age women were not tested during the same phase of the menstrual cycle, for practical considerations. The baseline and 3 month estradiol and follicle-stimulating hormone levels were similar, however, and any effects of testing during differing phases of the cycle during would be expected to diminish our ability to determine exercise effects on study parameters, including FMD. We did not measure endothelium-independent vasodilation, which has been shown previously not to change with exercise training.[23] Finally, a subset of subjects was on medications (previously prescribed for at least a month with no changes during the program) that might effect study parameters. Subgroup analyses, however, showed that benefits of exercise were apparent in these subjects, as was determined for the majority of participants not on these therapies.

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Table I

Baseline Characteristics and Testing Data for 72 subjects who completed *Keep the Beat* program participation

Parameter	Study Participants
Age in years (average, range)	45, 22-62
Women	58 (81%)
Caucasian	45 (62%)
African-American	17 (24%)
Asian	10 (14%)
Hypertension (blood pressure >160/90 mmHg) by	
history or exam	14 (19%)
Treated with medications	*14 (100%)*
Hypercholesterolemia (low-density lipoprotein cholesterol >160 mg/dL) by	
history or exam	18 (25%)
Treated with medications	*10 (56%)*
Diabetes mellitus (fasting glucose >125 mg/dL) by	
history or exam	6 (8%)
Treated with medications	*5 (83%)*
Cigarette smoking (current)	5 (7%)

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Table 2

Baseline and 3 month data for 72 subjects who completed participation in *Keep the Beat*

Parameter	Baseline	3 Months	P Value
Vital Signs			
Body mass index (kg/m2)	28.8 ± 7.0	28.5 ± 6.9	0.0565
Systolic blood pressure (mm/Hg)	117 ± 14	118 ± 13	0.4825
Diastolic blood pressure (mm/Hg)	73 ± 9	71 ± 9	**0.0478**
Resting heart rate (beats/min)	70 ± 10	69 ± 11	0.7814
Lab Values			
Total cholesterol (mg/dL)	189 ± 35	181 ± 36	**0.0131**
Low-density cholesterol (mg/dL)	122 ± 31	116 ± 32	**0.0044**
High-density cholesterol (mg/dL)	60 ± 14	58 ± 17	**0.0277**
Triglycerides (mg/dL)	109 ± 74	106 ± 69	0.5159
C-reactive protein (mg/dL)	3.5 ± 4.4	4.2 ± 6.9	0.4788
Glucose (mg/dL)	94 ± 23	95 ± 17	**0.0435**
Insulin (μunit/mL)	11 ± 8	12 ± 8	0.0687
Homeostasis model assessment of insulin sensitivity (HOMA Index)	2.67 ± 2.15	3.01 ± 2.63	0.1901
Estradiol * (pg/mL)	77 ± 76	72 ± 65	0.7567
Follicle-stimulating hormone * (IU/L)	28 ± 32	27 ± 30	0.7323
Endothelial and Progenitor Cell Testing			
Flow-mediated dilation (% change)	7.8 ± 3.4	8.5 ± 3.0	**0.0096**
Endothelial progenitor cell colonies/well	37 ± 47	54 ± 55	**0.0003**
CD 133/VEGFR-2 ** (cells/mL)	3 ± 4	19 ± 13	< **0.0001**
Treadmill Exercise Data (Bruce protocol)			
Exercise duration (sec)	544 ± 137	599 ± 143	**0.0001**
Peak heart rate (beats/min)	172 ± 13	174 ± 13	0.1672
Respiratory exchange ratio	1.2 ± 0.1	1.2 ± 0.1	0.9886
Peak oxygen consumption (mL O_2/kg/min)	28.7 ± 6.9	30.1 ± 7.0	**0.0028**
Ventilatory threshold	28.7 ± 3.3	29.7 ± 3.6	< **0.0001**
Anaerobic threshold	19.9 ± 3.9	19.7 ± 3.9	0.3068

* Women Only (N=58)

** Subset of Participants with Flow Cytometry Data (N=21)

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Table 3

Covariates as predictors of change in brachial artery flow-mediated dilation following 3 months of program participation, initially found significant in the stepwise model, then re-run using the general linear model with Type III sums of squares so that the P-value of each covariate reflects adjustment for all other covariates. All analyses were performed using the SAS statistical analysis package, utilizing the STEPWISE, GLM, and MEANS procedures (SAS User's Guide: Statistics, Version 9 Edition: SAS Institute Inc, Cary, NC). All reported P-values are based on two-sided t-tests.

Variable	P Value
Baseline flow-mediated dilation	< 0.0001
Change in low-density lipoprotein cholesterol	< 0.0001
Change in total cholesterol	0.0002
Change in diastolic blood pressure	0.0175
Age	0.0104
Change in colony-forming units	0.0377
Change in peak oxygen consumption (mL 0_2/kg/min)	0.0536