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Aerobic Exercise Improves Measures of Vascular Health in Diabetic Peripheral Neuropathy

Sandra A. Billinger[1], **Jason-Flor V. Sisante**[1], **Abdulfattah S. Alqahtani**[1], **Mamatha Pasnoor**[2], and **Patricia M. Kluding**[1]

[1]Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center

[2]Department of Neurology, University of Kansas Medical Center

Abstract

Aims—Aerobic exercise improves vascular endothelial function in people with Type 2 diabetes mellitus (T2DM). There is minimal information is available regarding vascular health in people with T2DM and diabetic peripheral neuropathy (DPN). Thus, the primary aim of this secondary analysis was to determine whether a 16-week aerobic exercise intervention could improve vascular health in people with T2DM and DPN. A secondary aim was to explore the relationship between changes in flow-mediated dilation (FMD) and the number of years since diagnosis of DPN.

Methods—We examined whether a 16-week aerobic exercise intervention would improve vascular health in people with T2DM and DPN. We used Doppler ultrasound to assess brachial artery diameter and peak shear at baseline and post-exercise. Paired t-tests were used to determine whether the outcome measures improved from baseline to post-intervention. Pearson correlation assessed the relationship between DPN (years) and the percent change score (pre- to post-intervention) for FMD.

Results—Seventeen individuals were included in the data analysis. After the intervention, peak diameter increased (3.9 (0.5) to 4.0(0.5) mm; $p = 0.07$). Time to peak shear occurred at 60.5 (24.6) seconds when compared to baseline at 68.2 (22.7) seconds; $p = 0.17$). We found that a longer duration (in years) of DPN demonstrated a fair, negative relationship ($r = -0.41$, $p = 0.19$) with the percent change in FMD.

Conclusion—Aerobic exercise was beneficial for improving measures of vascular health but these were not statistically significant. The magnitude of change may be affected by the duration of DPN.

Keywords

ultrasound; cardiovascular; diabetes; physical activity

Corresponding Author: Sandra A Billinger, University of Kansas Medical Center, 3901 Rainbow Blvd, MS 2002, Kansas City, KS 66160; 913-945-6685 (office); 913-588-6910 (fax) sbillinger@kumc.edu.

Conflicts of Interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

Introduction

People with Type 2 diabetes mellitus (T2DM) often present with impaired vascular endothelial function.(1–4) The vascular endothelium may be greatly affected by the chronic alterations in blood glucose regulation(5) and may be the result of advanced hyperglycemic damage.(6, 7) At rest, lower extremity blood flow was reduced in people with T2DM when compared to healthy controls when matched for age, gender, weight and fitness level.(7) However, these differences were not statistically significant. During a bout of exercise, the people with T2DM had significantly lower leg blood flow than the control group. The authors reported that those with T2DM had an impaired response to acetylcholine. These findings suggest that those with T2DM exhibit vascular endothelial dysfunction when the system is challenged such as physical exertion.

Aerobic exercise training has demonstrated a positive impact on vascular endothelial function in people with T2DM.(3, 8) Increasing shear stress such as during exercise is generally beneficial and may facilitate adaptive structural remodeling of the artery wall through these endothelium-mediated mechanisms.(9) One study implemented an 8-week aerobic exercise intervention in people with T2DM and age-matched controls. The study did not find adaptive arterial remodeling but reported improved vascular endothelial function within 2 weeks of the intervention and this improvement was maintained in both groups at 4, 6, and 8 weeks of the intervention.(3)

Exercise-induced improvements in vascular endothelial function in people with T2DM are encouraging, but less is known in people who have T2DM and diabetic peripheral neuropathy (DPN). One study investigated the relationship between vascular endothelial function of the brachial artery and the presence of neuropathy.(10) To assess endothelial function of the brachial artery the authors used a non-invasive technique called flow-mediated dilation (FMD). To determine the presence of neuropathy, the study examined sensory conduction velocity of the sural nerve and motor conduction velocity of the median nerve. The authors reported that FMD was positively and significantly related with both the sensory and motor conduction velocities. A negative association was found between duration of diabetes (in years) and FMD.

Thus, the primary aim of this secondary analysis was to determine whether a 16-week aerobic exercise intervention could improve vascular health in people with T2DM and DPN. Therefore, we hypothesized that our measures of vascular health would improve after the aerobic exercise intervention. A secondary aim was to explore the relationship between changes in FMD and 1) the number of years since diagnosis of DPN and 2) the change in neuropathy symptoms using the Total Neuropathy Score (TNS), which is a composite measure of peripheral nerve function that includes grading of signs/symptoms, nerve conduction studies, and quantitative sensory testing.(11)

Materials and Methods

Twenty people with diabetic peripheral neuropathy (confirmed by study neurologist) were enrolled into an aerobic exercise intervention study. Detailed information regarding the

aerobic exercise intervention and methodology used for confirmation of DPN has been described in detail in our previous work.(12) The original study was approved by the Human Subjects Committee at University of Kansas Medical Center. Institutionally approved written informed consent was obtained prior to study participation.

Individuals who were between 40–70 years of age, who were previously sedentary, were safe to participate (by physician medical release form), and reported a diagnosis of T2DM with symptoms of neuropathy were enrolled into the study. The symptoms of neuropathy were bilateral, chronic symptoms of numbness, pain or tingling in the feet. The 16-week aerobic exercise intervention was three times per week. Individuals started at 50% of VO_2 reserve (VO_2R) for 30 minutes and increased to 70% VO_2R.(12) Exercise time increased during the aerobic exercise intervention.

Flow Mediated Dilation (FMD)

We have reported our methodology for FMD.(12, 13) Participants were asked to refrain from food or caffeine for 12 hours and no vigorous activity for 24 hours prior to the FMD procedure. Data was collected between the hours of 7:30am and 9:30am and kept at similar times of day for each participant. Individuals were also asked to refrain from morning medications but were allowed to take them immediately after the FMD procedure. The participant rested supine for 20 minutes in a temperature controlled (22–24 degrees Celsius) and a quiet, dimly lit room.(13) Participants were not allowed to cross the legs at rest or during the procedure. However, if participants reported low back pain during supine lying, we placed a bolster under the knees for participant comfort. After the 20-minute rest period, blood pressure (BP) was taken. Heart rate (HR) was monitored continuously using a 3-lead EKG.

An automated cuff with rapid inflation system (D.E. Hokanson, Bellevue, Washington) was placed just distal to the olecranon process.(14, 15) We used a stabilizing device to allow for optimal scanning of the brachial artery and avoid arm movements during the ultrasound imaging. The brachial artery was identified longitudinally always at the same reference point, 2–3 cm proximal to the antecubital fossa using an ultrasound system and a 7.5 MHz linear array transducer (Siemens Medical Solutions, Malvern, Pennsylvania). Once a satisfactory image of the brachial artery was obtained, the transducer was stabilized using a custom-designed holder. We then marked the location of the ultrasound probe on the arm using a marker and measured the vertical and horizontal distance from the olecranon process to the probe to ensure identical placement of the probe at the post-intervention visit. We also saved the information from the ultrasound screen at the baseline study visit information for depth, frequency and insonation angle.

We captured Doppler velocity measurements at an insonation angle of 60 degrees using the ultrasound system. Baseline diameter and blood flow velocity was recorded continuously for 60 seconds after the 20 minutes rest period. Then the pneumatic cuff was inflated to suprasystolic pressure (220 mmHg) and maintained for 5 minutes. Twenty seconds prior to cuff deflation, recording of diameter and blood flow velocity was resumed. At 5 minutes, the cuff was deflated while ultrasound images continued to be recorded for an additional 3

minutes. All images were stored on a computer and analyzed off-line using specialized software (Brachial Analyzer, Medical Imaging Applications, Coralville, Iowa).

Data Analysis

We used paired sample t-tests to determine whether the measures of vascular health improved from baseline to post-intervention. Pearson correlation was used to assess the relationship between DPN (presence of neuropathy in years) and the percent change score (pre- to post-intervention) in FMD. We also wanted to assess whether the percent change score in FMD was related to the TNS change score. To understand the strength of the relationship of our selected outcome measures, we used criteria defined by Portney and Watkins:(16) Pearson's coefficient (r) = 0.00 – 0.25, little to no relationship; r = 0.25 – 0.50, fair relationship; r = 0.50 – 0.75, moderate to good relationship; and r >0.75, good to excellent relationship. P-values were considered significant at $p \leq 0.05$. All statistical analyses were performed using IBM SPPS® Statistics Software Version 20 (Armonk, New York).

Results

Seventeen individuals were included in the secondary analysis. Of the 20 enrolled participants, two withdrew from the study and 18 completed the 16-week aerobic exercise intervention. One participant's resting blood flow data (pre-cuff inflation) was not analyzable due to movement and not included in the secondary analysis. Participant characteristics are reported in Table 1. All outcome measures at baseline and post-intervention are summarized in Table 2. Resting baseline brachial artery diameter and shear stress was essentially unchanged after the intervention. We previously reported that percent FMD was significantly improved post-intervention.(12) The absolute mean difference in percent FMD was 2.1%, which is below a clinically relevant improvement of 3.6%.(17) Time to peak brachial artery dilation occurred 7.7 seconds faster post-intervention but this finding was not statistically significant. Peak diameter increased after the intervention but this was not statistically significant ($p = 0.07$).

We found that the amount of time (in years) DPN was present demonstrated a negative, fair relationship with the change in FMD ($r = -0.41$, $p = 0.19$). This suggests that the improvement in FMD after an aerobic exercise program may be negatively affected or blunted by the number of years with DPN. We report that the pre-to post-intervention improvement in the change score in FMD was fairly related to a decrease in the TNS ($r = -0.40$, $p = 0.13$).

Discussion

The major findings in this study were, first, that people with a history of T2DM and DPN demonstrate impaired FMD. Although not a primary aim of the study, we found that our reported values are similar to previously published values in people with T2DM and no DPN.(1, 3, 4, 10, 18) Second, a structured 16-week aerobic exercise intervention at moderate intensity beginning at 50% VO_2R and increased to 70% of VO_2R can improve vascular measures in people with DPN. Since brachial artery endothelial dependent dilation reflects

cardiovascular risk, our data suggest that moderate aerobic exercise may reduce cardiovascular risk by improving overall vascular health. Third, we demonstrate that the pre- to post-intervention change in percent FMD may be blunted by the duration of time diagnosed with DPN.

DPN and FMD

This study demonstrated that FMD is impaired in people with a diagnosis of DPN. We report baseline values for FMD were 5.0 ± 3.6%, which is similar to other reports in people with T2DM.(1, 3, 4, 10, 18) Our values for FMD were not surprising given the co-morbid cardiovascular conditions along with T2DM. Although this was not the primary focus of the secondary analysis, reporting these FMD measures is an important first step in this patient population. We did not include endothelial-independent vasodilation in our study procedures. Including endothelial-independent vasodilation would have provided insight on "vascular smooth muscle sensitivity to nitric oxide."(19) This is one limitation in our study since people with DPN have nerve damage.

Aerobic Exercise and FMD

The primary focus on this secondary analysis was to investigate whether a moderate-intensity aerobic exercise intervention can improve measures of vascular health in people with DPN. The majority of the literature supports aerobic exercise is beneficial for measures of vascular health in people with T2DM, but no information is available for those with DPN. We found that a 16-week aerobic exercise intervention improved FMD, peak diameter and the time to peak FMD. We previously reported a signficant improvement in FMD from baseline to post-intervention.(12) The magnitiude of improvement in FMD was lower than reported values from an 8-week combined aerobic and resistance exercise program in T2DM.(8) The authors reported extremely low baseline FMD values, 1.7% compared to 5.0% in our participants. Another potential reason may be due to the exercise training intensity prescribed. We prescribed beginning exercise at 50% VO_2R and increased to 70% during the 16 weeks. Maiorana and colleagues progressed aerobic exercise to participant tolerance for the first 3 weeks but then maintained aerobic exercise between 70–85% of HR reserve for the remaining weeks. Although the starting work rate was not clearly stated, the ending workrate was considered high intensity and may have resulted in a greater improvement in FMD. A recent study used an 8-week aerobic and resistance exercise training protocol(3) except the aerobic exercise training intensity was 70–75%HRR. At this work rate, the magnitude of change in FMD is similar but slightly less than our findings.

Differences in study procedures may account for the variability in the magnitude of change in FMD. All of our testing procedures were done at similar times of day in the morning (between 7:30am and 9:30am) following an overnight fast and study participants were asked to refrain from taking medications until after the procedure. The study by Maiorana and colleagues differs in a couple of ways.(8) First, individuals were allowed to take medications 4 hours prior to the FMD scan. Current recommendations for FMD procedures suggests medications should be witheld for at least 6 hours to avoid confounding effects on FMD.(15) If medications are not witheld for at least 6 hoursthen information regarding which drugs and time taken in proximity to the FMD scan is recommended. (15) Medications were not

listed so the influence of a specific drug(s) on vascular constriction or dilation is unknown. Second, the methodology for the study by Maiorana et al(8) for FMD was strain-gauge plethysmography versus Doppler ultrasound. While both methods are acceptable, these may account for differences in measures. Third, DPN is a complicaton of T2DM and can result in "slow peripheral nerve degeneration".(12) It is plausible that people with DPN may not respond as effectively to improved vascular function as healthy individuals or those with T2DM and no DPN. Future work should consider a randomized controlled trial to determine whether vascular function in people with DPN responds to a similar magnitude as people with T2DM.

DPN Measures and FMD

Since the presence of DPN can result in nerve degeneration,(12) this may have some effect on vascular measures including FMD. Aerobic exercise may be a therapeutic intervention targeted at improving symptoms of DPN. In a prior study of people with DPN, a 10-week aerobic exercise intervention improved neuropathic symptoms and increased the number of intraepidermal nerve fiber branching.(20) While a positive finding of the study, there was no mention of DPN duration in relationship to intraepidermal nerve fiber branching. Therefore, we wanted to examine whether a longer duration of DPN may have a negative impact such as blunting the response to an aerobic exercise intervention on FMD. This is the first study to address whether the years with DPN are related to changes in FMD after an aerobic exercise intervention. We report those with a longer the duration of DPN (in years) had less improvement in FMD following the 16-week exercise program. Although the findings were not statistically significant in this small sample, there is early evidence that the longer DPN exists, the less improvement in FMD. We recognized that this is subjective and the exact time point for DPN symptoms is unknown. Therefore we chose to use a valid and reliable(11) measure of peripheral nerve function to determine whether a change in the TNS would be related to change in FMD pre- to post-intervention.

Similar to the findings related to duration of DPN, we report an inverse relationship between the change in FMD and TNS. Thus, the decrease in TNS score (improvement in symptoms) demonstrated a fair relationship with improved FMD score ($r = -0.40$, $p = 0.13$). While previous work demonstrated improved pain rating and neuropathic symptoms after aerobic exercise,(20) this study extends the findings by using a more comprehensive composite assessment of neuropathy and examining vascular function (FMD). A limitation of this current study was not assessing non-endothelial dependent vasodilation. This assessment would have provided information related to smooth muscle response to a vasodilator such as nitroglycerin. Using this technique would have provided a more complete picture of vascular health in those with DPN. Future work needs to further examine whether both endothelial-dependent and endothelial-independent vasodilation are impaired in people with DPN and the contribution to peripheral vascular health. This is a secondary analysis of the parent study(12) and acknowledge the small sample size is a limitation of the study. Since the parent study was an exploratory study to determine safety of aerobic exercise in people with DPN, we are not powered to detect changes in the vascular outcome measures and the results should be interpreted with caution. Finally, aerobic exercise has demonstrated improvements in intraepidermal nerve fiber branching(20) and now we demonstrate

improvements (although not statistically significant) in measures of vascular health. An area of future work to be considered is whether changes in FMD and intraepidermal nerve fiber branching are improved to a similar magnitude after an aerobic exercise intervention.

Conclusion

In conclusion, we found that a 16-week aerobic exercise program can improve measures of vascular health in people with DPN. We found improvements in peak arterial diameter and faster response time to peak dilation. However, the absolute mean different in percent FMD was 2.1%, which is below a clinically relevant improvement of 3.6%. We also report that people with DPN can improve measures of vascular health but the improvements may be blunted by duration and severity of DPN.

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Table 1

Characteristics of the study population at baseline

Variable	Number or Group Mean (SD) (n = 17)
Male/female	4/13
Race/ethnicity	
White non-Hispanic	8
Hispanic	6
Black non-Hispanic	3
Age (years)	58.1 (5.1)
Years with diabetes	14.7 (6.4)
Years with neuropathy	6.8 (4.0)
Resting SBP (mmHg)	136.6 (13.9)
Resting DBP (mmHg)	76.9 (7.9)
Total neuropathy score	11.9 (5.6)
HbA1C (%)	7.6 (2.0)

SD = Standard deviation; SBP = Systolic blood pressure; mmHg = Millimeters of mercury; DBP = Diastolic blood pressure; HbA1C = Glycated hemoglobin

Table 2

Vascular health measures pre- and post-intervention

	Pre-intervention	Post-intervention	p-Value
Pre-cuff inflation			
Vessel diameter (mm)	3.6 (0.6)	3.6 (0.5)	0.27
Shear	223.0 (80.9)	217.6 (64.5)	0.48
Post-cuff deflation			
Percent FMD [12][1]	5.0 (3.6)	7.1 (4.5)	0.01
Peak diameter (mm)	3.9 (0.5)	4.0 (0.5)	0.07
Time to peak diameter (s)	68.2 (22.7)	60.5 (24.6)	0.17
Peak shear	435.8 (115.7)	411.9 (117.5)	0.22

[1]Percent FMD has been previously reported. Values are means (standard deviation) unless otherwise noted.

FMD = Flow-mediated dilation; mm = Millimeters; s = Seconds.