Treadmill Aerobic Training Improves Glucose Tolerance and Indices of Insulin Sensitivity in Disabled Stroke Survivors
A Preliminary Report

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Background and Purpose—Insulin resistance and glucose intolerance are highly prevalent after stroke, contributing to worsening cardiovascular disease risk and a predisposition to recurrent stroke. Treadmill exercise training (T-AEX) increases aerobic capacity (VO₂ peak) in chronic stroke patients, suggesting intensity levels that may be adequate to improve glucose metabolism. We compared the effects of a progressive T-AEX intervention to an attention-matched stretching intervention (CONTROL) on glucose tolerance and indices of insulin sensitivity in stroke survivors.

Methods—Participants had hemiparetic gait after remote (>6 months) ischemic stroke. They were randomized to 6-month T-AEX or a duration matched reference CONTROL program of supervised stretching exercises. Main outcome measures were glucose and insulin responses during a 3-hour oral glucose tolerance test (OGTT).

Results—Forty-six subjects (T-AEX=26, CONTROL=20) completed OGTT testing before and after the interventions. T-AEX increased VO₂ peak (+15% versus −3% Δ, P<0.01) compared with CONTROL. There were significant reductions in fasting insulin (−23% versus +9% Δ, P<0.05) and the total integrated 3-hour insulin response (−24% versus +3% Δ, P<0.01) in T-AEX compared with CONTROL. In patients with abnormal glucose tolerance at baseline, T-AEX resulted in a significant 14% decrease in 3-hour glucose response (n=12, P<0.05). Fifty-eight percent of T-AEX participants with abnormal baseline OGTT (7 of 12) improved glucose tolerance status at 2 hours compared with <10% (1 of 11) of impaired CONTROLS (P<0.05).

Conclusions—These preliminary findings suggest that progressive aerobic exercise can reduce insulin resistance and prevent diabetes in hemiparetic stroke survivors. Larger clinical trials are needed to definitively establish the use of structured exercise training for stimulating metabolic improvement poststroke. (Stroke. 2007;38:2752-2758.)

Key Words: diabetes • exercise • glucose intolerance • insulin resistance • stroke

The high prevalence of insulin resistance after stroke is central to poor cardiovascular health outcomes and sustained high risk for myocardial infarction and recurrent stroke in this population. The prevalence of insulin resistance exceeds 50% for nondiabetic individuals in the subacute stroke recovery phase. Insulin resistance and associated hyperinsulinemia are linked to vascular and hemodynamic abnormalities, and a prothrombotic state, conferring high population attributable risk for stroke and myocardial infarction. Hyperglycemia is also a primary mechanism linking diabetes and the prediabetic state to worsening cardiovascular risk, as prolonged exposure to glucose results in accelerated atherosclerosis secondary to a large number of observed cellular changes in vascular tissues. Combined prevalence of impaired glucose metabolism and type 2 diabetes mellitus (T2DM) is nearly 80% for individuals with chronic hemiparetic stroke. Prospective studies show that indices of insulin resistance independently predict increased first-ever stroke, whereas impaired glucose tolerance (IGT) and T2DM convey a 2- and 3-fold increased risk for recurrent stroke, respectively.

The high prevalence of insulin resistance and abnormal glucose metabolism after stroke may be partially mediated by profound cardiovascular deconditioning. Several studies show a ∼50% reduction in peak fitness levels among stroke survivors compared with age-matched individuals. Secondary abnormalities in hemiparetic body composition and tissue characteristics including gross muscular atrophy, increased intramuscular fat content, elevated tu-
mTOR necrosis factor-α, and over-expression of the fast myosin heavy chain muscle molecular phenotype may also contribute to an insulin resistant state.

It is possible that exercise training can alter these metabolic abnormalities in stroke-disabled individuals, similar to what is seen in nonstroke populations. This randomized study tests the hypothesis that treadmill exercise training (T-AEX) will improve glucose tolerance and indices of insulin sensitivity in individuals with chronic hemiparetic stroke, compared with a control group (CONTROL) of stroke volunteers performing supervised stretching exercise.

Materials and Methods

Study Participants
Men and women >45 years of age with chronic (≥6 months) hemiparetic gait after ischemic stroke were recruited from The Baltimore Veterans Affairs Medical Center, University of Maryland Medical System, the James Lawrence Kernan–University of Maryland Rehabilitation Hospital, and through outside advertising for participation in a randomized exercise intervention trial. This study reports findings in a subset of subjects (n = 46) from a larger randomized stroke exercise study. Volunteers were included in the analysis based on successful completion of a 3-hour oral glucose tolerance test (OGTT) before and after the 6-month intervention.

Participants had completed all conventional physical therapy and had residual mild-moderate hemiparetic gait deficits, defined as asymmetry of gait with reduced stance, or reduced stance and increased swing in affected limb, with preserved capacity for ambulation with assistive device (eg, walker or cane) or standby ability. Baseline evaluations included medical history and examination, ECG, blood chemistries and counts, Mini-Mental State Examination, and Center for Epidemiological Studies Depression Scale. Exclusion criterion included heart failure, unstable angina, peripheral arterial occlusive disease, history of diabetes, and apathy operationally defined as incapacity to follow 2-point commands, dementia, untreated major depression, and other medical conditions precluding participation in treadmill aerobic exercise training. After screening and baseline testing, volunteers were randomized to 6 months (3 times per week) of either progressive T-AEX or a reference control exercise program of supervised stretching (CONTROL). Participants were randomized to T-AEX or CONTROL after baseline testing using a blocked allocation schema and a computer-based pseudo-random number generator. Age and severity of deficits were considered in the randomization design, because imbalance in these factors could confound analyses. Therefore, separate blocked randomizations were performed according to age (<65 versus ≥65 years) and gait deficit severity indexed by self-selected walking speed (<0.44 m/s versus ≥0.44 m/s), given the potential impact of these factors on rehabilitation outcomes.

Exercise Testing
A treadmill tolerance test at no incline was first performed to assess gait safety and select walking velocity for subsequent peak exercise testing and training. Participants minimized handrail support, and a gait belt was worn for safety. After a 15-minute rest, those completing ≥3 consecutive minutes treadmill walking at ≥0.1 m/s (≥0.2 MPH) proceeded to constant velocity progressively graded exercise testing to volitional fatigue. Eligible patients were those achieving adequate exercise intensities without signs of myocardial ischemia or other contraindications for participating in aerobic training. After a 1-week rest interval to avoid effects of fatigue at baseline, exercise testing with open circuit spirometry was conducted to measure VO2 peak, using a graded submaximal treadmill test as previously described. Peak aerobic testing was repeated at the 6-month postintervention time point.

Oral Glucose Tolerance Testing
The OGTT was performed at baseline and after 6-month T-AEX or CONTROL. After a 12-hour overnight fast, participants underwent a 3-hour OGTT to measure fasting glucose and insulin, and the total insulin and glucose responses to glucose load. An intravenous catheter was placed to facilitate blood sampling and, after a 15-minute rest, 2 baseline blood samples (5 mLs) were drawn before 75 g glucose ingestion. Subsequent blood samples were drawn every 30 minutes for 3 hours. All plasma samples were frozen (−70°C) and pre-post samples were analyzed in duplicate for glucose (glucose oxidase method, YSI instruments) and insulin by radioimmunoassay (Linco) in the same assay to avoid intra-assay variability. The average of the 2 values was used in the statistical analyses.

Body Composition
Weight (kg) and height (cm) were measured in duplicate, and BMI (kg/m²) calculated. Fat mass and lean tissue mass were determined by Dual-energy X-ray absorptiometry (DXA, Model Prodigy, LUNAR Radiation Corp, Analysis version 7.53.002).

Exercise Intervention Protocols
The T-AEX protocol consisted of three 40-minute sessions per week at a target aerobic intensity of 60% to 70% heart rate reserve, determined according to the Karvonen equation, performed over a 6-month training period. Training started at low intensity (40% to 50% heart rate reserve) for 10 to 20 minutes and gradually progressed to target levels. Because these highly deconditioned individuals were initially incapable of continuous exercise, they started with discontinuous training and advanced by 5 minutes per 2 weeks as tolerated. Handrail and harness support as well as heart rate monitoring by 2 lead ECG (Polar Electro) were used throughout, and vital signs recorded before, during, and after each exercise session.

The CONTROL protocol provided matched duration exposure to healthcare personnel, implementing components of conventional physical therapy common to stroke. Patients performed 13 targeted active and passive supervised stretching movements of the upper and lower body 3 times per week for 30 to 40 minutes over 6 months.

Data Analysis
The total integrated and incremental (above basal) insulin and glucose responses were quantified by calculating area under the curve using the trapezoidal method. The homeostasis model for insulin resistance (HOMA-IR) was calculated using the established formula, (fasting insulin [µU/mL]×fasting glucose [mmol/L]/22.5). Repeated measures ANOVA was used to predict values of outcome variables across time. In cases where group-by-time interaction was significant, within-group time point comparisons were made. Pearson correlation coefficients were used to assess the strength of relationship between insulin/glucose area change and changes in VO2 peak, body composition, and initial values. Finally, the Fisher exact nonparametric statistical test was used to determine whether the proportion of those with abnormal baseline glucose tolerance who changed status across training was different between groups. Data are expressed as mean±SE. A 2-tailed P<0.05 was considered significant.

Results
Participant Characteristics
Sixty-nine hemiparetic stroke volunteers underwent baseline OGTT testing and were randomized to either T-AEX or CONTROL (Figure 1). Forty-six of these completed a second OGTT after the intervention (T-AEX=26, CONTROL=20). Twenty-three dropped out because of noncompliance or medical issues unrelated to the study. There were no significant clinical or demographic differences between T-AEX...
and CONTROL completers including age (63±9 versus 62±10 years), BMI (27±4 versus 29±6 kg/m²), body weight (78.6±2.5 versus 82.2±3.0 kg), percent body fat (36.8±1.9 versus 35.6±2.1), fat free mass (45.9±2.2 versus 48.6±1.9 kg), and VO₂ peak (13.7±0.9 versus 14.8±1.1 ml/kg per minute). Gait deficit severity indexed by 10-m self-selected floor-walking velocity was similar in T-AEX (0.54±0.29, range 0.13 to 1.17 m/s) and CONTROL (0.59±0.27, range 0.12 to 1.10 m/s), representing a broad range of mobility impairment. Assistive devices for ambulation were used by 77% in T-AEX and 75% in CONTROL. The percentage of women in the T-AEX and CONTROL groups was 50% and 35%, respectively. Blacks represented 46% of the group in T-AEX and 55% in CONTROL with the remainder being nonhispanic whites. Forty-six percent in T-AEX and 55% in CONTROL had abnormal OGTT at baseline based on 2-hour glucose value. Specifically, of the 12 with abnormal OGTT in T-AEX, 8 had IGT and 4 had T2DM. In CONTROL, 8 had IGT and 3 had T2DM.

Effects of T-AEX Versus CONTROL on VO₂ Peak and Body Composition
There was a 15% gain in peak VO₂ with T-AEX compared with a 3% decrease in CONTROL (P<0.01; Table 1). There were no significant changes in body weight, %fat, or fat free mass in the T-AEX or CONTROL groups after the intervention.

Effects of T-AEX Versus CONTROL on Insulin and Glucose Responses
There was a significant reduction in fasting insulin with T-AEX compared with CONTROL (−23% versus +9%, P<0.05; Table 2), but no change in fasting glucose in either group. Similarly, there were significant reductions in both total (−24% versus +3%; Table 2, Figure 2) and incremental (−25% versus 0%; Table 2) insulin areas during 3-hour OGTT with T-AEX compared with CONTROL, but no significant change either between or within groups in 3-hour glucose response. Between group differences in insulin area reduction remained after covarying for small changes in weight and body composition (% fat, and fat free mass) over time. There was a significant reduction in HOMA-IR within the T-AEX group, but the between-group comparison only approached significance (−25% versus +16%, P<0.07).

The change in insulin area during the intervention period was inversely related to the change in VO₂ peak in the 2 groups combined (r=−0.34, P<0.05), but not to body weight or fat mass. There was a strong inverse relationship

| Table 1. Peak Fitness and Body Composition Change Across Intervention in T-AEX vs CONTROL |
|---------------------------------|-----------|-----------|-----------|-----------|
|                                | Treadmill (n=26) | Control (n=20) |                                     |
|                                | Baseline 6 Months | Baseline 6 Months | P, Group-by-Time Interaction |
| VO₂ Peak, ml/kg per min        | 13.7±0.9 15.7±1.1* | 14.8±0.9 14.4±1.0 | 0.002 |
| Body weight, kg                | 78.6±3 78.5±2 | 82.2±3 81.9±3 | 0.44 |
| Body fat, %                    | 36.8±2 37.4±2 | 35.6±2 35.9±2 | 0.76 |
| Fat free mass, kg              | 45.9±2 46.3±2 | 48.6±2 48.4±2 | 0.54 |

Values are mean±SE.
*Significant between-group effect.
between change in insulin area and baseline insulin area across the intervention in the T-AEX group ($r = -0.65$, $P<0.01$), indicating that the most hyperinsulinemic subjects at baseline had the greatest improvement with exercise training. As with insulin response, there was a strong relationship between change in 3-hour glucose area over time in T-AEX and the baseline 2-hour glucose level ($r = -0.59$, $P<0.01$). However, there was no significant correlation between change in glucose area and change in VO$_2$ peak. Neither glucose area nor insulin area change were significantly related to changes in body weight, % fat, or fat free mass.

**Glucose and Insulin Area Responses in Subjects With IGT and T2DM**

The 12 subjects in the T-AEX group with abnormal glucose tolerance at baseline (8 IGT and 4 T2DM) lowered their glucose area response with exercise training by 14% (1688 ± 72 to 1455 ± 98 mmol/L per 180 minutes; $P=0.05$; Figure 3), whereas those T-AEX participants with normal glucose tolerance (n = 14) at baseline showed no significant change in the glucose response (1106 ± 48 to 1197 ± 69 mmol/L per 180 minutes) during OGTT. Comparison of the responses in the abnormal (n = 12) versus normal (n = 14) glucose tolerance subgroups within T-AEX across time demonstrated a significant between-group difference ($P<0.01$), indicating that only those with abnormal OGTT had a reduced glucose area in response to exercise training. This contrasts with the 11 CONTROLS with abnormal glucose tolerance (8 IGT and 3 T2DM), in whom there was no change in the glucose area response across the intervention period (1573 ± 72 to 1545 ± 49 mmol/L per 180 minutes, $P=0.05$ not significant). In contrast to what was seen in T-AEX, when the abnormal and normal glucose tolerance subgroups within CONTROL were compared statistically across time, there was no difference in glucose area response change. Furthermore, when the glucose area response change in the abnormal subgroup from T-AEX (n = 12) was compared with that of the abnormal subgroup in CONTROL (n = 11) there was a trend toward between-group significance for glucose area ($P=0.08$).

Seven of the 12 (58%) with abnormal baseline glucose tolerance in the T-AEX group improved their glucose tolerance status after 6 months of exercise training, whereas only 1 of 11 (9%) in CONTROL experienced similar benefit. Specifically, 5 of the 8 with IGT at baseline reverted to normal status, whereas 2 of the 4 with T2DM reverted to IGT status after T-AEX. In CONTROL, 1 of the 8 with IGT reverted to normal, and none of the 3 with T2DM changed status. The proportion of those in T-AEX versus CONTROL

| Table 2. Effects of 6 Months T-AEX and CONTROL on Glucose and Insulin Measures |
|-------------------------------|------------------|------------------|------------------|------------------|
|                               | Treadmill (n=26) | Control (n=20)   | $P$, Group-by-Time Interaction |
|                               | Baseline        | 6 Months        | Baseline        | 6 months        |
| Fasting glucose, mmol/L       | 5.3 ± 0.1       | 5.2 ± 0.1       | 5.4 ± 0.1       | 5.4 ± 0.1       | 0.64 |
| Fasting insulin, pmol/L       | 102 ± 9         | 79 ± 5*         | 96 ± 6          | 105 ± 9         | 0.04 |
| 3-hour glucose area, mmol/L per 180 min | 1375 ± 71     | 1346 ± 61       | 1456 ± 57       | 1452 ± 44       | 0.78 |
| Total 3-hour insulin area, pmol/L per 180 min | 104 512 ± 8741 | 79 338 ± 5764* | 95 918 ± 8343 | 98 506 ± 7996 | 0.01 |
| Incremental 3-hour insulin area, pmol/L per 180 min | 86 245 ± 8178 | 65 012 ± 5245* | 80 145 ± 8113 | 80 451 ± 8347 | 0.03 |
| HOMA-IR                       | 4.0 ± 0.4       | 3.0 ± 0.3       | 3.7 ± 0.3       | 4.3 ± 0.7       | 0.07 |

Values are mean ± SE. *Significant between group effect.

Figure 2. Change in the mean insulin curve across 6 months within the T-AEX group (n=26). *There were significant differences between groups at the 60-, 90-, 120-, and 150-minute time points ($P<0.01$). Values are mean ± SE. Units are pmol/L. Open squares represent baseline measurements at each time point and closed squares are the postintervention measurements.
who changed status across time was significantly different by Fisher exact test ($P<0.05$).

Insulin area change was not different according to baseline glucose tolerance status, as evidenced by lack of a significant difference in response between abnormal T-AEX (114 455±50 091 to 90 114±29 722 pmol/L per 180 minutes, $n=12$) and normal T-AEX (95 989±39 085 to 70 102±26 734 pmol/L per 180 minutes, $n=14$). Similarly, subgroup analysis did not show significant differences between groups for HOMA-IR.

**Discussion**

Insulin resistance and glucose intolerance are increasingly recognized as prospective, independent risk factors for stroke and cardiovascular disease. $^{1,4}$ This preliminary report is the first to show that progressive treadmill aerobic exercise training improves glucose tolerance and indices of insulin sensitivity in older individuals disabled by stroke. We show significant reductions in the insulin response to glucose load in the T-AEX group but not in CONTROL, and significant lowering of fasting insulin with a trend toward a between-group difference in the reduction of HOMA-IR. There was a significant reduction in glucose area with T-AEX in the subgroup with abnormal baseline glucose metabolism (IGT or T2DM) compared with no change with T-AEX in subjects with normal glucose tolerance or CONTROLS. In general, stroke subjects with greater degrees of insulin resistance and glucose intolerance improved the most after 6-month T-AEX. These initial findings suggest that it is possible to reverse IGT and T2DM with T-AEX after stroke, thereby potentially reducing cardiovascular and recurrent stroke risk. Larger clinical trials are needed to confirm these preliminary findings and establish the long-term health benefits of exercise for individuals with disability after stroke.

A decrease in insulin response during OGTT is seen in nonstroke individuals after exercise training at moderate intensities. Aerobic training lowers fasting plasma insulin and reduces the magnitude of insulin response to oral glucose load with no change in glucose tolerance in lean and obese healthy individuals. $^{23-25}$ Research using the euglycemic clamp confirms a significant improvement in insulin sensitivity with exercise training, independent of changes in weight or body composition among healthy, older individuals. $^{26}$ The decrease in insulin response to oral glucose without concomitant changes in glucose response suggests greater tissue sensitivity to circulating insulin. Our data provide evidence of reduced fasting and postload hyperinsulinemia as indices of improved insulin sensitivity that is comparable in magnitude to that seen in nonstroke populations.

Glucose response during OGTT showed no improvement with T-AEX training when considering the entire group ($n=26$). However, subgroup analysis demonstrated that those with abnormal baseline glucose tolerance (IGT or T2DM) showed a 14% reduction in postload glucose area that was significantly greater than normal T-AEX participants. This study further showed that 58% with abnormal baseline glucose tolerance improved their status with T-AEX versus 9% of CONTROL, which was significantly different between groups. The effects of structured exercise training on glucose control has previously been studied in IGT and T2DM, but ours is the first to demonstrate the effect in disabled stroke survivors with limited exercise capacity. Boule et al$^{27}$ published a meta-analysis showing beneficial effects of exercise training on glucose control. Physical activity or structured exercise training used alone or in combination with diet and medication form the foundations of therapy for T2DM and the metabolic syndrome. $^{28}$ The Diabetes Prevention Program $^{29}$ reports that lifestyle intervention, including moderate intensity exercise for 150 minutes per week, decreases the incidence of progressing from IGT to T2DM by 58% over a 2.8-year follow-up, making it more effective than metformin administration for preventing progression to diabetes in nonstroke high risk elderly. Similarly, our preliminary findings show that structured physical activity may reduce indices of insulin resistance and improve glucose tolerance in the disabled stroke population. This is especially relevant given the high prevalence of abnormal glucose metabolism after stroke. $^{10}$
The mechanisms for exercise-mediated improvement in insulin and glucose responses among stroke survivors are under investigation in our laboratory. Unique biological features in hemiparetic muscle may contribute to insulin resistance, thus representing potential metabolic targets for improvement with an exercise intervention. These include gross muscular atrophy with hemiparetic mid-thigh CT scans showing 20% lower muscle area and increased intramuscular fat area, a finding strongly associated with insulin resistance and its complications. In addition, we have previously shown striking increases in myosin heavy chain proportions toward the less-insulin sensitive fast (type II) muscle molecular phenotype, and 3-fold elevated tumor necrosis factor-α transcript levels in hemiparetic skeletal muscle, which blocks insulin signaling and is linked to insulin resistance and diabetes. When considering all participants, we observed a relationship between change in peak fitness and insulin area across the intervention period. Further studies are needed to understand the optimal dose-intensity and underlying molecular mechanisms by which exercise improves glucose metabolism and insulin sensitivity in chronic hemiparetic stroke.

Epidemiological studies suggest that insulin resistance, as measured by fasting hyperinsulinemia, is related to risk of ischemic cardiac events, carotid intima-media thickening, and stroke. In addition, prospective investigation shows postload insulin areas during OGTT predict risk of future stroke. Notably, a study involving almost a thousand Scandinavian men showed that those in the highest quintile of OGTT insulin area had a 2-fold relative risk of stroke than those in the lowest quintile of insulin area. Thus, epidemiological research based on surrogate measures of insulin sensitivity provide powerful evidence that insulin resistance is strongly associated with increased risk for stroke and cardiovascular events. In addition, postload hyperglycemia, independent of fasting levels, has emerged as the more important contributor to atherosclerotic disease. Postload glucose levels, assessed by OGTT, more strongly predict macrovascular complications according to data compiled in nonstroke populations. For individuals with history of stroke or transient ischemic attack, IGT and T2DM prospectively predict a 2- and 3-fold increased risk for recurrent cerebrovascular events, respectively. Hence, a variety of evidence provides strong rationale for investigating the use of structured physical activity to improve glucose control and hyperinsulinemia for tertiary prevention of stroke.

The strengths of this study are its randomized design, attention matched control group, and absence of change in weight or body composition across the intervention period, enabling us to isolate the effects of T-AEX on glucose and insulin measures in this group of stroke survivors. The groups were well-matched for baseline OGTT status and for degree of disability. The profile of gait deficit severity in both groups was broad and representative of the typical community dwelling hemiparetic stroke patient, with approximately three quarters of participants requiring an assistive device for ambulation.

Our results are limited by small sample size and potential for recruitment bias. Uneven dropout rates across training, with 41.2% attrition in CONTROL compared with only 25.7% in T-AEX, constitutes another potential source of bias in the comparative analyses. This small hospital-based intervention study is inadequate to determine the proportion of community dwelling stroke survivors capable of producing exercise-induced metabolic improvements of this magnitude. Whether structured and sustainable exercise programs could be made available through community translation to improve cardiovascular-metabolic health in this high risk population is an important unanswered question. Finally, this study was limited by having not been designed to track longitudinal cardiovascular health outcomes or to determine the potential for exercise to prevent the progression of insulin resistance to frank diabetes.

**Summary**

This randomized study provides the first evidence that exercise can improve glucose intolerance and indices of insulin sensitivity in chronically disabled stroke survivors. These findings extend to the stroke population consensus recommendations for exercise to optimize management of insulin resistance and diabetes, and support American Stroke Association guidelines for exercise after stroke. Larger clinical trials are needed to evaluate the effectiveness of exercise for improving cardiovascular-metabolic health outcomes and in tertiary prevention of stroke.

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**Disclosures**

None.

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