**Abstract**

**Background:** Pre-diabetes has deleterious effects on cognitive and physical health, yet responds favorably to exercise. Little is known about how exercise affects health in African Americans, a group disproportionately affected by pre-diabetes and type 2 diabetes. The objective of this pilot study was to evaluate the effects of an aerobic training (AT) versus resistance training (RT) program on cognitive function and biomarkers of type 2 diabetes (T2D) and Alzheimer’s disease (AD) in African American elders with pre-diabetes.

**Methods:** Fifteen African Americans aged 50 years and older with pre-diabetes were randomly assigned to a 6-month AT or RT protocol. Pre- and post-intervention, participants were administered cognitive tests. Blood biomarkers of T2D and AD were also examined.

**Results:** Group differences in cognitive test performance or biomarkers failed to reach statistical significance (all p-values > 0.05). Exploratory within group analyses to examine change over time indicated an improvement in verbal memory in the AT group (p=0.03), and an increase in high-density lipoprotein levels (p=0.01) and a trend decrease in plasma levels of Aβ42 (p=0.10) in the RT group.

**Conclusion:** Although there were no overall group differences in cognitive or biomarker outcomes in this small pilot study, within group differences point to a potential benefit of AT on verbal memory and RT on lipid profiles in older African Americans with pre-diabetes. Larger exercise trials in African Americans are needed to advance our understanding of how different exercise modalities affect cognitive and cardiovascular health in older African Americans, a group at high risk for cognitive decline.

**ABBREVIATIONS**

T2D: Type 2 Diabetes; AT: Aerobic Training; RT: Resistance Training; HbA1c: Glycosylated Hemoglobin

**INTRODUCTION**

Pre-diabetes, a prodromal stage of type 2 diabetes (T2D) characterized by higher than normal blood glucose levels [1], disproportionately affects African Americans [2]. Studies show African Americans may be more insulin resistant than Whites, independent of diabetic status, thus suggesting African Americans may be predisposed to T2D [3]. Pre-diabetes is also a risk factor for future cardiovascular events [4], and cognitive impairment...
and dementia [5]. Underlying pathological mechanisms implicated in the relation between poor glucose regulation and cognitive impairment includes cerebral micro-vascular and macro-vascular damage [6], and increased AD neuropathology [7].

Higher levels of aerobic activity are associated with more efficient glucose regulation in older adults with [8] and without T2D [9]. Increased aerobic activity in older adults has been shown to improve cognition, namely executive function, and favorably modulate biomarkers associated with dementia [9-11]. Much of the prior research on exercise has focused on the effects of aerobic exercise on cognitive health in White populations and little is known about the effects of exercise on cognitive function in minority populations. Resistance training (RT) may confer greater benefits on glycemic control and body composition than aerobic training (AT) in African Americans with T2D [12]. Researchers in this study also observed racial differences in pancreatic α-cell function in response to RT, with African Americans showing greater improvement, an indicator of improved insulin secretion [12]. The reasons for racial differences in response to RT are unclear. One possible explanation may relate to racial differences in body composition, in particularly mean differences in lean muscle mass and adiposity between African Americans and Whites. African Americans have a higher proportion of lean muscle mass than Whites [13-15]. Resistance training increases lean muscle mass, an insulin sensitive tissue important for glucose disposal [16], with favorable consequences for basal metabolic rate and thus insulin sensitivity. Thus, RT may a particularly effective strategy to improve insulin sensitivity and glucose control in African Americans. Similar to effects reported for AT, RT has been shown to yield cognitive benefits in older adults [17,18].

No study to date has examined the effects of AT and RT programs on cognition and biomarkers of T2D and AD among African American elders. A better understanding of the relative benefit of different exercise modalities on glycemic control, cognitive function, and biomarkers of T2D and AD in African American elders, a group at high risk for T2D and cognitive impairment, may help inform the development of effective strategies to address racial disparities in T2D and dementia. In this pilot study, we examined the effects of structured 6-month AT versus RT program on cognition, and T2D- and AD-related biomarkers in sedentary African American elders with pre-diabetes.

MATERIALS AND METHODS

Study Design and Sample

Prospective participants were recruited from the local community through advertisements in newspapers, health presentations at local churches and community centers, and by providing a blood pressure checks at a predominately African American senior center. Inclusion criteria included self-report of African American race, age between 50-89 years, pre-diabetes as defined by American Diabetes Association HbA1C criteria [1], and sedentary status. Sedentary status was defined as self-report of <30 minutes of structured physical activity <3 times per week in the last 6 months. Exclusion criteria included unstable cardiac disease, significant cerebrovascular disease, musculoskeletal impairment, or presence of other medical conditions with significant psychiatric, neurologic, or metabolic sequelae. Use of statins or anti-hypertensive agents was permitted, while use of diabetes medications was not. Baseline sample characteristics are provided in (Table 1). The institutional review board of the University of Washington and the Veterans Administration of Puget Sound approved this study.

Procedures

Participants were randomized to an AT or RT group using research randomizer software. Cognitive testing and 12-h fasting blood collection occurred between 8am and 10am at baseline and month 6. Study visits were conducted in the community at a local senior center with a high population of African American elders as members.

Exercise Interventions

Participants in both groups exercised 4 days per week for 45-60 minutes per session for 6 months. Participants were instructed to maintain their normal caloric intake for the duration of the study. Exercise sessions were conducted at local Young Men’s Christian Associations (YMCA) facilities. Participants received individualized supervision by a certified fitness trainer for the first 8 exercise sessions. Thereafter, the trainer supervised 1 session every other week. Compliance was measured as days per week exercised divided by the number of weeks in the program.

Participants in the AT group received heart rate (HR) monitors and engaged in high-intensity aerobic activity under the supervision of the trainer. The details of this program are published elsewhere [19]. The RT group completed a full-body progressive program consisting of 3 days per week and one day per week of stretching. The RT days included the following procedure: one day of upper body exercises, one day of lower body exercises, and one day of various exercises targeting major upper and lower body muscles. Participants engaged in 2-3 sets of 10-15 repetitions. Every 8 weeks participants were trained on a new set of exercises. A5 repetition max (5-RM) test was conducted to determine baseline training weight and increases in training weight every 4 weeks. The RT group is modeled after American College of Sports Medicine and American Heart Association exercise recommendations for older adults [20], and previous reports [21].

Cognitive Function

Executive function was measured using the Trail-Making Test [22], Symbol-Digit Modalities test [23], and Dot Counting [24]. Verbal memory was measured using Story Recall [25,26] and the Buschke Selective Reminding Test [27] were administered.

Assays

Plasma Aβ40 and Aβ42 levels were determined using high-sensitivity human enzyme-linked immunosorbent assay (ELISA, EMD Millipore, Billerica, MA). Plasma brain-derived neurotrophic factor (BDNF), plasma vascular endothelial growth factor (VEGF) and plasma insulin-like growth factor 1 (IGF-1), levels were quantified using Quantikine ELISA (R&D Systems, Minneapolis, MN). Plasma insulin levels were quantified.
using radioimmunoassay (Axis-Shield Diagnostics, Dundee, United Kingdom). Plasma glucose was measured using Glucose Colorimetric Assay (Cayman Chemical Company, Ann Arbor, MI). Cholesterol levels were measured using enzymatic colorimetric Roche Cobas c 501 assay (F. Hoffman-La Roche, Ltd, Basel, Switzerland), and low-density lipoprotein (LDL) cholesterol concentrations were calculated using Friedewald’s formula. All assays were performed in duplicate and we report the mean of the two measurements per sample.

**Statistical Analysis**

Cognitive outcomes reflected as difference scores (month 6- baseline), were subjected to separate analysis of variance (ANOVA) by cognitive domain (i.e. composite measures of executive function and memory), with exercise group as the independent variable. Age, education, and BMI were statistically considered for inclusion as covariates in the model. The EF composite included summed z-scores for symbol-digit, dot counting (number correct) and Trails B performance. The memory composite included Bushke delayed free recall, category recall, phonemic recall, story recall immediate (verbatim), and story recall delayed (verbatim). Secondary analyses examined the effects of exercise condition on T2D and AD biomarker variables. Exploratory tests examining pre-and-post differences (paired t-tests) in outcome measures were performed when appropriate. Positively skewed distributions were log-transformed prior to analysis.

**RESULTS AND DISCUSSION**

Fifteen participants (AT group=8, RT group=7) were included in primary analyses, details describing the study flow from initial contact through study completion are provided in (Figure 1). (Table 1) shows participants in the two groups were not significantly different in age, gender, education, blood pressure, HbA1C, fasting plasma glucose, use of beta blockers, and global cognitive function. The AT group (M=3.46, SD=0.88) and RT group (M=3.45, SD=0.67), t (13) =0.01, p=0.98) did not differ in compliance rates.

Between group differences in cognitive test performance did not reach statistical significance (all p-values>0.05). There was a trend for improved EF performance in the RT group relative to the AT group (F_{1,14}=3.98, p=0.06). Similarly group differences in biomarker data was not significant (all p-values>0.05), although there was a trend for decreased Aβ-42 in the RT group (F_{1,14}=4.16, p=0.06). Within group comparisons showed improvement in immediate verbal recall (p=0.03) in the AT group; for the RT group there was an increase in HDL (p=0.01). There was also a trend for a decrease in Aβ-42 after the intervention (p=0.10) in the RT group.

This pilot feasibility study examined the effects of a structured AT versus RT on cognitive function on T2D-and AD-related biomarkers in sedentary African American elders pre-diabetes. We did not find significant group differences in cognitive test performance or biomarker outcomes. Preliminary evidence from within group comparison showed verbal memory performance responded favorably to AT, and cholesterol levels to RT. (Table 2) provides details on exercise treatment effects.

Cognitive abilities mediated by prefrontal brain regions have been shown to be the most responsive to exercise interventions [9,18,28,29], and vulnerable to the effects of pre-diabetes [30]. Surprisingly, we found no significant between groups or within group effects for exercise on executive function performance. Our study differs from others that report improvement in executive function in several ways. We did not include a direct marker of cardiorespiratory fitness; therefore we could not whether changes in cardiorespiratory fitness occurred, a key mediator of cognitive function [31]. Our participants also engaged in bimonthly supervised training with a certified trainer, while other studies provided more supervision to participants. It is possible that our samples differed in intensity of training during unsupervised training sessions and this may have played a role in our null findings. Our RT protocol differed in intensity and duration from that of Liu-Ambrose and colleagues [28]. Findings from their study suggest that longer-term exercise interventions may be needed for cognitive benefits.

Evidence supporting exercise effects on memory in humans is inconsistent. Our findings are similar to previous reports demonstrating favorable effects of AT on memory in older adults [32] and older adults with memory impairment [33]. In contrast, other studies report no effect of AT on memory [9,19]. Differences in study design and participant characteristics may be a factor in these disparate findings. We found RT was associated with an increase in HDL levels. Previous studies show HDL levels respond favorably to AT [34,35]. The effects of RT only regimens on lipid profiles are less consistent. Tucker and colleagues [36] reported a positive association between RT and lipid profiles in older adults; however this study implemented an epidemiological design and included only male participants. Other RT intervention studies report no association with HDL [37,38]. Our study differs from previous RT studies as we included older both men and women with different baseline health profiles. Gender and ethnoracial racial differences in lipid profiles have been reported; with a
Table 1: Subject Characteristics According to Group Allocation.

<table>
<thead>
<tr>
<th></th>
<th>Aerobic (n=8)</th>
<th>Resistance (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.5±2.9</td>
<td>58.5±6.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Sex, male (n)</td>
<td>2</td>
<td>1</td>
<td>X2=1.00</td>
</tr>
<tr>
<td>Education, years</td>
<td>15.1±2.2</td>
<td>14.8±2.5</td>
<td>0.83</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.7±1.6</td>
<td>29.1±1.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Taking β-blocker, (n)</td>
<td>3</td>
<td>3</td>
<td>X2=1.00</td>
</tr>
<tr>
<td>SBP</td>
<td>130.6±16.3</td>
<td>131.4±13.2</td>
<td>0.91</td>
</tr>
<tr>
<td>DBP</td>
<td>78.8±7.7</td>
<td>80.1±6.1</td>
<td>0.73</td>
</tr>
<tr>
<td>HbA1C</td>
<td>5.8±1.3</td>
<td>5.8±2.1</td>
<td>0.98</td>
</tr>
<tr>
<td>FPG</td>
<td>93.6±9.8</td>
<td>100.7±11.0</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Abbreviations: Mean±SD; MMSE = Mini Mental State Examination; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HbA1C = Hemoglobin A1C; FPG = Fasting Plasma Glucose; X2 = Chi Square Statistic

Table 2: Baseline Subject Characteristics and Treatment Effects on Physiological Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Aerobic (n=8)</th>
<th>Resistance (n=7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, m²/kg</td>
<td>33.1±6.6</td>
<td>33.4±0.4</td>
<td>32.0±6.7</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>5.8±0.1</td>
<td>8.6±12.6</td>
<td>5.8±0.21</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>91.6±9.8</td>
<td>86.8±12.6</td>
<td>91.7±9.6</td>
</tr>
<tr>
<td>FPI, μU/mL</td>
<td>15.9±8.2</td>
<td>15.2±10.1</td>
<td>15.3±8.9</td>
</tr>
<tr>
<td>Chol, mg. dl</td>
<td>182.8±19.4</td>
<td>181.2±24.5</td>
<td>210.0±52.8</td>
</tr>
<tr>
<td>HDL, mg. dl</td>
<td>58.2±8.7</td>
<td>57.8±4.8</td>
<td>69.3±13.0a</td>
</tr>
<tr>
<td>LDL, mg. dl</td>
<td>108.4±17.5</td>
<td>105.7±21.1</td>
<td>122.3±53.5</td>
</tr>
<tr>
<td>TG, mg. dl</td>
<td>81.7±36.8</td>
<td>89.2±48.0</td>
<td>91.6±50.5</td>
</tr>
<tr>
<td>IGF-I, ng/ml</td>
<td>103.1±36.7</td>
<td>99.5±26.1</td>
<td>100.7±18.2</td>
</tr>
<tr>
<td>VEGF, pg/ml</td>
<td>32.5±17.1</td>
<td>39.8±43.5</td>
<td>62.1±47.4</td>
</tr>
<tr>
<td>AB40, pg/mL</td>
<td>343.4±3064.4</td>
<td>539.0±4503.0</td>
<td>486.0±3665.6</td>
</tr>
<tr>
<td>AB42, pg/mL</td>
<td>131.0±19.8</td>
<td>138.0±27.5</td>
<td>124.7±22.7</td>
</tr>
</tbody>
</table>

Abbreviations: Note: *p<0.05; a=within group; b= between groups; Mean±SD; BMI= Body Mass Index; HbA1C= Hemoglobin A1C; FPG= Fasting Plasma Glucose; FPI= Fasting Plasma Insulin; Chol= Total Cholesterol; HDL= Fasting Plasma High Density Lipoprotein Concentration; LDL= Fasting Plasma Low Density Lipoprotein Concentration; TG= Fasting Plasma Triglycerides Levels; IGF-I = Fasting Plasma Insulin-Like Growth Factor 1; VEGF= Plasma Vascular Endothelial Growth Factor; BDNF= Plasma Bone-Derived Growth Factor; AB40= Fasting Plasma Levels of Aβ40; AB42= Fasting Plasma Levels of Aβ42.

recent report showing African Americans had the lowest odds of having low HDL or high triglycerides in comparison to other ethnoracial groups [39]. Based on our preliminary findings, it is plausible that ethnoracial difference in lipid profiles may be related to different metabolic responses to exercise.

Limitations to this study include our small sample size, unbalance gender representation, and stringent study inclusion criteria. However, it is important to note, small sample sizes are not uncommon in exercise interventions [9,12]. Despite these limitations, this pilot study adds to the existing literature. Our study advances the existing scientific knowledge by including African American elders, a group underrepresented in clinical intervention research. By including African Americans, we increase knowledge of how different exercise regimens may benefit other segments of the aging population. Our attention to the cognitive and physiological consequences of RT is also noteworthy, as previous work has focused mostly on the health benefits of AT [9,19].

CONCLUSION

We have shown here that exercise studies are feasible, and can be done in a community setting, and show promise for studying outcomes related to T2D and AD in older African American. Results from this study will help generate hypotheses regarding different cognitive and metabolic responses to AT and RT in African American elders. The current study design could serve as the basis for future studies, with larger sample sizes, to determine the optimal exercise prescription to promote cardiovascular and cognitive health in minority elders, a group at increased risk for vascular risk factors associated with cognitive decline and dementia.

ACKNOWLEDGMENTS

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REFERENCES


