Effect of Aerobic Exercise on HbA1c and Cognitive Function in Prediabetes Patients with Mild Cognitive Impairment

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Abstract

Objective: This study aimed to investigate the effects of moderate to high-intensity aerobic exercise on HbA1c (Glycated hemoglobin), FBS (fasting blood sugar) and cognitive function in mild cognitive impairment prediabetes patients.

Materials and Methods: Seventeen elderly mild cognitive impairment (age 55-70) men and women were selected and were randomly divided into 2 groups as aerobic (n=10) and control (n=10). Six subjects were excluded during the study. Finally, 14 subjects were continued the exercise program. Assessments were done at baseline and 12 weeks after intervention. The 12-weeks aerobic exercise program consisted of 90 min sessions in length 3 days per week under the supervision of the exercise specialist. Cognitive function, HbA1c, and FBS were evaluated. The differences in all variables (one way ANOVA), correlation (Pearson single correlation) and relative changes between baseline and 12 weeks (paired T-tests) were investigated.

Results: HbA1c, FBS decreased significantly in the aerobic group whereas cognitive function increased significantly after 12 weeks aerobic (*P*-value< 0.05 for all). Also, the change of cognitive function was significantly associated with a change of FBS (r= -0.84) after a 12-week aerobic exercise (*P*-value: 0.011). Differences between groups in HbA1c, FBS and cognitive function (Mini-Mental State Examination) were not significant.

Conclusion: Aerobic exercise may improve HbA1c, FBS and subsequently cognitive function in prediabetes elderly subjects. Therefore, a decrease in glycemic indicators could lead to improve cognitive function.

Keywords: Glycated hemoglobin A1c, Fasting blood sugar, Aerobic exercise, Mild cognitive impairment

Introduction

A lot of studies have been performed to determine the association between diabetes and dementia (1,2). However, The dependency on diabetes and cognitive decline are not well studied (1).

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Diabetes is an identified risk factor for cognitive impairment and dementia (3,4). Although, the pathophysiologic mechanisms sustaining these associations are not well clear (3), but recognizing the risk factors of the cognitive impairment could help screening who may benefit from early intervention. (1,5).

Glycosylated hemoglobin is an important glycemic control indicator that illustrates an average of three months of blood glucose prediction (6). It is noticeable that increasing the level of HbA1c is highly associated with cognitive performance in middle-aged and older individuals (7). Moreover, In comparing to fasting plasma glucose, it is not clear whether HbA1c can provide more information about the cognitive function (8).

Due to the well-known effects of adiposity on insulin sensitivity and resistance, losing weight is key to prevent and control diabetes (9). Also, exercise training is a proven part of type 2 diabetes treatment. On the other hand, numerous clinical trials in type 2 diabetes patients, illustrated that structured exercise training improves coronary vessel disease (CVD) risk factors and glycemic control (10, 11) According to WHO, not enough physical activity may be considered as one of the foremost causes of mortality and disability throughout the world. However, exercise has an essential effect on blood glucose levels and therefore plays a significant role in the treatment of diabetic patients. On the other hand, various earlier investigations revealed that regular exercise training significantly reduces the values of HbA1c (12).

It has been well documented that regular exercise plays an important role in preventing and management of dementia by reducing the risk of T2DM (13). Aerobic exercise training has been recommended as the most appropriate form of exercise form which has a lot of positive metabolic effects, including reduced fasting blood sugar (FBS) levels (14) and also brain atrophy in older adults (7). On the other hand, it has been proved that exercise can improve cognitive function. However, most of the studies conclude to this, have been on healthy older adults, and therefore the applicability of these findings to older adults who are at high risk of cognitive decline and diabetes are not well documented. Also, there are few studies that have investigated the effects of exercise on cognitive function, HbA1c, and FBS (and whether exercise has a beneficial effect on the improvement of these three items) in prediabetes patients with mild cognitive impairment (15). The available guidelines for this matter are remarkably general and do not contain necessary information about duration, intensity, or most beneficial type of exercise for mentioned subpopulations to maximize the benefit while preserving minimal risk (16). To the best knowledge of present authors, not many studies directly investigated the effects of aerobic exercise on cognitive function, FBS and HbA1c (16). Therefore, this study aims to investigate the effects of 12 weeks of moderate to high aerobic exercise program on cognitive function, HbA1c, and FBS in prediabetes patients with mild cognitive impairment.

Materials and Methods

This research is a pilot study and was performed at the Shiraz university sports center and Imam Reza Cardiovascular Clinic, Shiraz, South Iran between October 2018 and January 2019. We selected 20 male and female patients with mild cognitive impairment (age 55-70) and were randomly divided into two groups as aerobic (n=10) and control (n=10). Three subjects were excluded during the study due to chest pain (n=1), job reason (n=2) and not have regular participation (n=3). Inclusion criteria in this study were as follows: subjects should have type 2 diabetes or prediabetes, they should not have regular physical activity from six months before the beginning of the research, they should not have the respiratory disease and heart failure and also do not have surgery for at least 6 months. The subjects selecting and their characteristics have been considered in Figure1 and Table1

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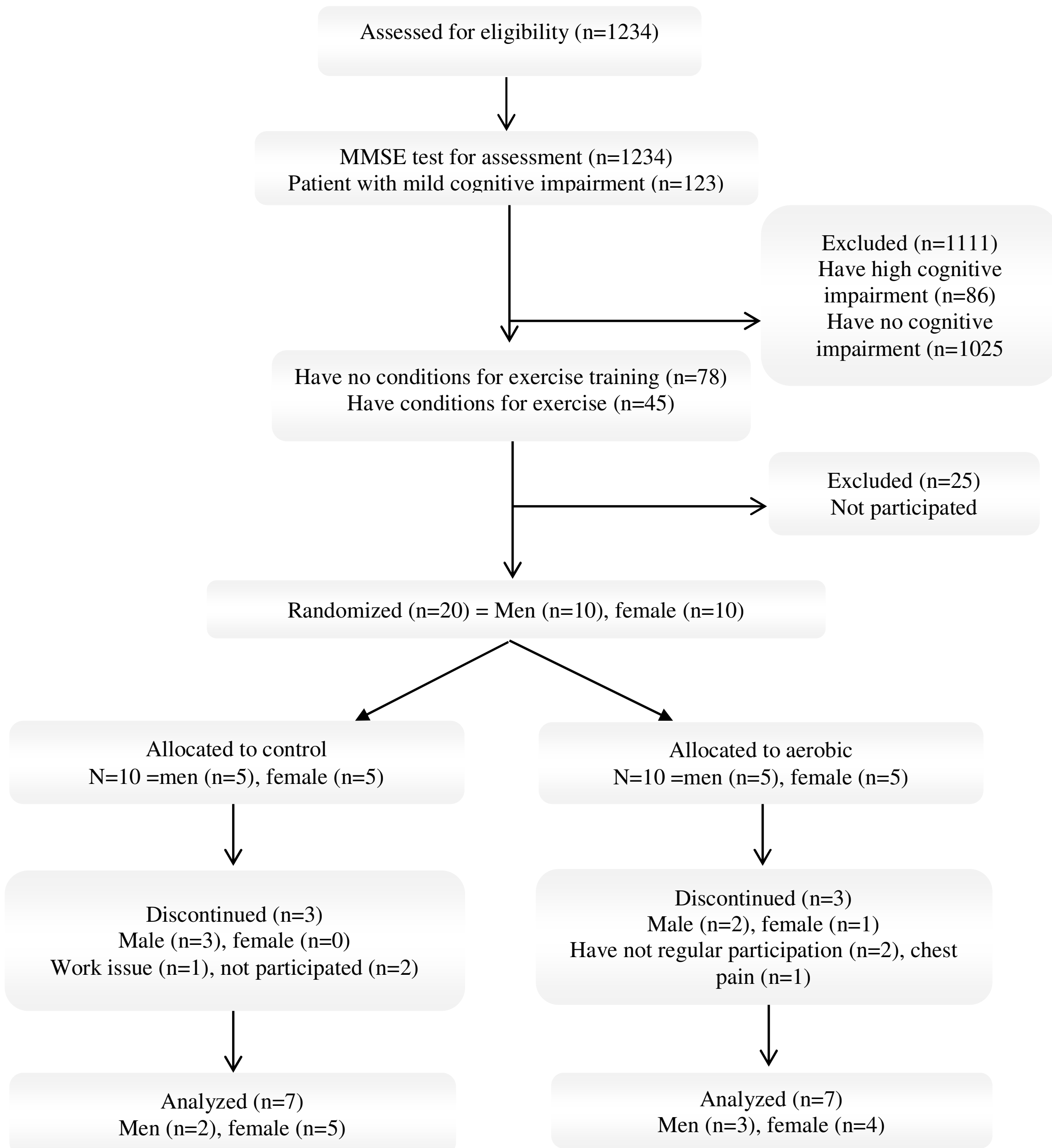

Figure 1. Selecting the subject flow diagram.

Table 1. The studied patients characteristics at baseline (n= 14)

Variable	Control (n=7)	Aerobic (n=7)
Male/female (n)	2/5	3/4
Age (y)	66.79 (±2.50)	65.4 (±2.93)
Height (cm)	157.41 (±4.45)	156.85 (±2.71)
BMI (kg/m^2)	28.61 (±1.83)	26.2 (±1.09)
HR (beats/min)	82.33 (±2.81)	73.57 (±2.37)
Systolic BP (mmHg)	132.5 (±3.00)	116.8 (±3.50)
Diastolic BP (mmHg)	83.3 (±3.30)	81.5 (±2.50)

Note. Data are mean ± SD, BMI = body mass index; HR=heart rate,

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Aerobic exercise
The 12 weeks aerobic exercise program consisted of 90 min sessions in length 3 days per week. The first two weeks were considered for compatibility with exercise. Each session included a 10 minutes warm-up before and the same period cool-down after the exercise program, 10 minutes of aerobic games with mental challenges (Design by author), various walking methods for 15 min, 15 min walking on a treadmill,10 min cycling on cycle ergometer, 5 min stopper, 5 min kayak and 10 min for rest undertook progressive (moderate to high) intensity (60–85% of VO2 PEAK) 3 days per week (weeks 3-5; 60% of vo2 peak, weeks 6-8; 70% of vo2 peak, weeks 9-12; 85% vo2peak) (17).

Cognitive assessment
The cognitive function was assessed with the Mini-Mental State Examination (MMSE). The MMSE is a neuropsychological test (18). This examination has been widely used and according to this test, we can recognize cognitive impairment if the MMSE score, was 24 or less (9). The MMSE includes 11 questions and the test time is 5-10 minutes. The maximum score in MMSE is 30 and the questions are asked to the subjects and then scored. For any score, less than 25, suspect some degree of cognitive impairment (18). The MMSE is formed into two segments. The first part that has a maximum score of 21 consists of memory, addresses orientation and attention. The second part that has a maximum score of 9 includes, assessment of the ability of the participant to name, verbal commands and follow written, copy a complex polygon, and write a sentence. Most of the studies have used the MMSE as an instrument to evaluate cognitive impairment, and evidence has shown that the MMSE is a multidimensional instrument to recognize the cognitive function that includes attention, memory, concentration, language, and orientation (19). Seyedian et al by using the ROC curve showed that a cut-off point of 22 illustrated a sensitivity of 90 and specificity of 93.5 percent (20).

Biochemical parameters
Blood samples were collected between at baseline and 12 weeks after a 12 h overnight fasting for testing levels of FBS and HbA1c and sent to the biochemistry department at the Shiraz Hafez hospital, Iran for laboratory analysis. The glucose oxidase method, using Eco-Pak glucose reagent was implemented to measure the blood glucose. Moreover, HbA1c was determined by utilizing the immunoturbidimetric method which measured the absorbance of the HbA1c fraction and total hemoglobin fraction at 415 nm.

Statistical analysis
To examine group differences, data presented as mean ± SD were analyzed using a one-way analysis of variance (ANOVA). Relationships of cognitive function, FBS and HbA1c were evaluated by Pearson's single correlation test (10). To detect differences between pre and post time points, the paired T-tests were performed. For statistical analysis, Statistical Package for the Social Sciences (SPSS) ver. 22 (SPSS Inc, Chicago, IL, USA) was utilized. Statistical significance was set at P-value<0.05 (21).

Ethical considerations
Ethical approval was obtained from the ethics review board of the Institute of Physical Education and Sport Sciences (Code: IR.SSRC.REC.1397.019) and IRCT code: IRCT20181001041198N1.

Results
Subject characteristics at baseline are shown in Table 1.

Effects of aerobic exercise on cognitive function, HbA1c, body weight, and FBS:
After 12 weeks of aerobic exercise, cognitive function improved significantly (P-value: 0.007). Also, we observed that body weight, FBS and HbA1C decreased at 12^{th} week compared with baseline and this reduction was significant in FBS (P-value: 0.01), body

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weight (p-value: 0.03) and HbA1C (*P*-value: 0.01). (Table2)

FBS, HbA1C and cognitive function differences between groups:

There was no significant observed difference between control and aerobic groups in cognitive function (MMSE), FBS and HbA1C.

Associations of FBS, HbA1C and cognitive function (MMSE) at baseline:

At baseline, there were no meaningful correlations observed between FBS, HbA1C and cognitive function (MMSE). (Table3)

Relationships between changes in FBS, HbA1C and cognitive function (MMSE):

After 12 weeks aerobic exercise, decreased in FBS was associated with increased in cognitive function (*P*-value: 0.01, r= 0.84). Also decreased in body weight was associated with increased in cognitive function (*P*-value: 0.01, r= 0.84). There were no meaningful correlations between HbA1C and cognitive function (MMSE). (Table4)

Discussion

This research investigated the effects of a 12 weeks aerobic exercise training on cognitive function, FBS, HbA1c and body weight in elderly prediabetes with mild cognitive impairment. The main finding of this research

Table 2. The absolute changes in cognitive function, HbA1c, body weight, and FBS after 12 weeks

Variable	Baseline	12 weeks	Difference	*P*-value
HbA1c %				
Aerobic (n=7)	5.81 (±0.08)	5.06 (±0.20)	0.75 (±0.21)	0.013*
Control (n=7)	5.79 (±1.56)	5.76 (±1.45)	0.03 (± 0.11)	0.625
FBS (mg/dL)				
Aerobic (n=7)	101.28(±6.31)	77.14 (±1.56)	24.14 (±6.46)	0.011*
Control (n=7)	99.00 (±10.80)	98.50 (±10.08)	0.50 (±0.25)	0.660
MMSE				
Aerobic (n=7)	25.7 (±0.80)	28.1 (±0.50)	-2.42 (±0.61)	0.007*
Control (n=7)	23.60 (±3.55)	23.42 (±2.60)	0.18 (±0.95)	0.585
Body Weight (kg)				
Aerobic (n=7)	66.40 (±1.68)	65.51 (±1.90)	0.88 (±0.31)	0.032*
Control (n=7)	72.20 (±6.20)	71.80 (±6.98)	0.40 (±0.78)	0.574

Abbreviations: HbA1C: Glycated hemoglobin; FBS: Fasting Blood Sugar, MMSE: Mini-Mental State Examination Statistically significant difference within the group from baseline is indicated by *P*-value< 0.05 and *. Values are the mean and standard deviation of the mean (aerobic= 7, control: n= 7). The paired t-tests were performed to detect differences between time points (pre and post).

Table 3. Partial Correlations of FBS, HbA1c and cognitive function (MMSE) at baseline

Variable	Body weight		MMSE	
	r	*P*-value	r	*P*-value
Aerobic group:				
FBS (mg/dL)	-0.43	0.33	0.44	0.31
HbA1c %	0.25	0.58	-0.09	0.84
MMSE	-0.66	0.10	-	-

Note: MMSE= Mini-Mental State Examination, FBS= Fasting blood sugar, HbA1C= Glycated hemoglobin, * = significant. Evaluated by Pearson's single correlation test.

Table 4. Relationships between changes FBS, body weight, HbA1c and cognitive function (MMSE). N=7

Variable	Body weight		MMSE	
	r	*P*-value	r	*P*-value
Aerobic group:				
FBS (mg/dL)	-0.16	0.72	0.84	0.01*
HbA1c %	-0.11	0.65	0.004	0.99
MMSE	0.84	0.01*	-	-

Note: MMSE= Mini-Mental State Examination, FBS= Fasting blood sugar, HbA1C= Glycated hemoglobin, * = significant. Evaluated by Pearson's single correlation test.

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was that the 12 weeks aerobic exercise training increased cognitive function simultaneously with decreasing FBS, HbA1C and body weight in elderly prediabetes women and men with mild cognitive impairment.

Relationship between HbA1c, FBS, cognitive function and body weight after 12 weeks' exercise:

To our knowledge, the studies about the effect of exercise training on the association of cognitive function and glycemic indicators are rare.

In this study, we demonstrated that decrease in HbA1c (nonsignificant) and FBS (r= 0.84 and *P*-value: 0.01) after 12 weeks of aerobic exercise was simultaneous with an increase in cognitive function. According to this, we can conclude that it seems a decrease in HbA1C and FBS was an independent risk factor for the future mild cognitive impairment in prediabetes elderlies. So according to these results, we can conclude that a further decrease in HbA1c and FBS leads to a greater increase in cognitive function. In the early stages of diabetes, cerebral neuropathological changes begin, which is with decreasing cognitive performance (24). According to some studies in literature, in comparison with healthy adults, abnormal blood glucose which is a characteristic of both prediabetes and type 2 diabetes is directly associated with increased risk of cognitive impairment (25). Hence, regular exercise has the ability of therapeutic effects on the cognitive function which is jeopardized by cognitive decline (such as Alzheimer's Disease) and type 2 diabetes (26). On the other hand, several other studies which in those who performed aerobic training or aerobic training plus diet control were not reported such a relationship between cognitive function and glucose changes (25). However, some previous studies which evaluated groups without diabetes were mainly focused on aerobic exercise and linked it to enhanced executive function (27). It is noticeable that adults with abnormal fasting blood glucose could show very early cognitive impairment (26). In comparison with non-diabetic individuals, mental speed and flexibility reduced in patients with type 2 diabetes (28). The mechanisms that lead diabetic patients to cognitive impairment are not fully understood. At the cellular level, fluctuations in glycemia have been shown more adversely affect endothelial function and in comparison to sustained hyperglycemia, cause oxidative stress (29), which potentially leads to more cerebrovascular damage and cognitive decline.

Different researches reported that nominally by increasing the level of HbA1c cognitive function would be improved (30). Some studies demonstrated a noteworthy faster cognitive decline in diabetic than whom with normoglycemia (31). However, studies show inconsistency in the relationship between prediabetes and cognitive decline. As an example, Tuligenga et al stated no significant acceleration in cognitive decline in prediabetes people than those with normal HbA1C levels (5). Against that, Rawlings et al stated cognitive decline significantly accelerated in people with prediabetes than those with normoglycaemia (31). Therefore the second type of results confirms our opinion that HbA1C and FBS levels are critical to prevent cognitive decline within both direct and indirect mechanisms (32). So according to the identification of the results of pre-diabetic individuals is necessary to prevent cognitive impairment.

This study is one of the rare studies in elderly men and women that examine the influence of aerobic exercise on the association between cognitive function, HbA1c, FBS and body weight. It is noticeable that the present study was non-invasive research for examining the effectiveness of exercise preventing cognitive impairment concerning HbA1c, FBS and bodyweight reduction. However, it had several limitations. It is difficult to find patients who simultaneously have mild cognitive impairment and prediabetes, so we could not find more patients with such characteristics. Moreover, due to the small sample size, it was not possible to examine the influence of gender on the effect of regular exercise on this

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mentioned. Furthermore, the limitations include the short duration of the study and also sample size (mentioned above); any mentioned factor could have changed the results of the investigation. Therefore, to realize the influence of exercise on HbA1c, FBS, cognitive function and body weight, a larger sample size over a longer period of training is required. Also, we could not measure the postprandial blood glucose. Finally, the patients' diet was out of control due to their physical condition.

Conclusions

In conclusion, aerobic exercise training may improve cognitive function after improving HbA1c, FBS in mild cognitive function patients. According to this, HbA1c and FBS levels are important factors for the prevention of cognitive impairment and hence we can conclude that the HbA1c and FBS reduction are independent risk factors for the future cognitive impairment in the elderly and the aerobic exercise is suitable for prediabetes elderlies with mild cognitive impairment.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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