Physical Activity Participation May Offset Some of the Negative Impact of Diabetes on Cognitive Function

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Objective: Diabetes increases an individual's risk of developing dementias (eg, vascular), whereas regular physical activity has been shown to lower this risk. The purpose of this study, therefore, was to examine the relationships among cognitive function, exercise status, and type 2 diabetes (T2 DM) to determine whether physical activity participation offsets any of the increased risk of cognitive dysfunction frequently associated with diabetes.

Measurements: A total of 145 subjects, 71 controls (Con) and 74 with T2 DM (DM), were studied using 2 cognitive tests (Mini-Mental State Exam [MMSE], and the Saint Louis University Mental Status exam [SLUMS]); the Even Briefer Assessment Scale for Depression (EBAS-DEP); the Harvard Alumni Physical Activity Questionnaire (HAPAQ); the Modified Barthel Index (MBI); and fasting insulin, glucose, glycated hemoglobin, and lipid levels.

Results: The presence of diabetes had a negative impact on at least one measure of cognitive function (MMSE), even though such function was fairly intact in most subjects (29.3 $\pm$ 0.1 Con, 28.7 $\pm$ 0.2 DM, $P < .05$). MMSE scores were significantly inversely associated with fasting insulin levels and insulin resistance (HOMA-IR), and longer duration sitting was associated with elevated blood glucose levels. Although "regular exerciser" status per se was not indicative of higher mental function, MMSE and SLUMS cognitive function scores were significantly associated with specific physical activity submeasures, including a positive association with hours spent doing light exercise on weekdays and an inverse relationship with weekend sitting (SLUMS only). SLUMS scores were also positively associated with a greater duration of weekend moderate exercise, while hours of weekend sitting were associated with higher blood glucose levels and depression.

Conclusions: Certain types of physical activity, including light and moderate exercise, appear to be beneficial to mental function in individuals with T2 DM. Having diabetes, particularly when less well controlled, is associated with lower cognitive function scores, and physical activity participation may prevent some of the potential decline in cognition. **(J Am Med Dir Assoc 2008; 9: 434–438)**

Keywords: Cognitive function; dementia; physical activity; exercise; type 2 diabetes

The available epidemiological data are somewhat inconclusive with regard to the exact contribution of type 2 diabetes (T2 DM) to cognitive impairment and dementias, including Alzheimer's disease (AD) neurodegeneration.[1] However, it is well established that T2 DM is associated with decreases in cognitive function.[2–4] Indeed, the presence of T2 DM may result in a 2- to 3-fold higher risk of developing various types of dementia, and older individuals with diabetes have an elevated risk for vascular brain damage and neurodegenerative changes.[5]

Conversely, physical activity decreases insulin resistance (IR) and the risk of vascular complications while improving glycemic control in diabetic individuals. Most of the advantages of physical activity may result from improved insulin action.[6–8] Participation in leisure time physical activities also reduces the risk of dementia,[9] and all levels of exercise participation may prevent or slow cognitive decline and possibly vascular dementias and AD.[10–12]

Although diabetic individuals experience a greater risk of vascular disease and alterations in blood glucose, insulin, and amyloid metabolism that increase their likelihood of dementias,[13] it remains unclear whether the benefits conferred by regular physical activity can offset these risks and prevent or reduce declines in cognitive function. The purpose of this study, therefore, was to examine the relationships among cognitive function, exercise status, and diabetes to determine if physical activity can offset the decline in cognitive function frequently associated with T2 DM.

METHODS

A total of 145 subjects, ages 36 to 86 years, 74 with T2 DM (DM) and 71 nondiabetic controls (CON), participated in

Old Dominion University, Norfolk, VA (S.R.C., C.T.S., S.R.S.).

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this study after giving their written consent. Prior to their enrollment, the study was approved by the Institutional Review Board at Old Dominion University. All subjects reported to the laboratory in the morning where they underwent a fasting blood draw and were given a battery of tests. The testing included 2 cognitive ones (Mini-Mental State Exam [MMSE] and the Saint Louis University Mental Status exam [SLUMS]), a depression scale (the Even Briefer Assessment Scale for Depression [EBAS-DEP]), and physical activity (Harvard Alumni Physical Activity Questionnaire [HAPAQ]) and activities of daily living (the Modified Barthel Index [MBI]) questionnaires. Subjects completed a slightly modified (for diabetes) version of the HAPAQ.[14]

After administration of the MMSE and SLUMS by an investigator, subjects answered the 3 other scales and questionnaires on their own, with incomplete or conflicting information resolved by an investigator with the subjects' input. For the purposes of classification, "regular exercisers" were defined (using the HAPAQ) as subjects engaging in at least 30 minutes of moderate aerobic exercise 3 times a week for a minimum of 1 year, while sedentary subjects engaged in 2 or fewer days of activity or activities of daily living (ADL) alone.

Fasting blood work was analyzed for insulin, glucose, glycated hemoglobin (HbA_{1c}), and lipid levels, and the results were used to verify the diabetes status of the subjects and to assess their overall glycemic control. American Diabetes Association clinical guidelines for diabetes diagnosis were used[15]: DM, fasting glucose ≥126 mg/dL; insulin resistant, 100 to 125 mg/dL; nondiabetic, <100 mg/dL. In addition, the HOMA-IR method was used to determine the degree of each subject's whole body insulin resistance (via fasting plasma glucose and insulin measurement).[16] HbA_{1c} values were determined on a DCA 2000 (Siemens, Deerfield, IL). Lipid levels, including total cholesterol, cholesterol subfractions (LDL and HDL), and triglyceride levels, as well as plasma glucose, were analyzed using the Cholestech LDX (Cholestech, Hayward, CA).

Results are presented as mean ±SEM for age, glycated hemoglobin, fasting glucose, and other lab tests. The cut-off points for MMSE scores (<24) and SLUMS (<20 for high school educated, <15 for less education) were used as the diagnosis of "dementia" in community samples, as has been done previously.[17,18] The EBAS-DEP cut-off point of a score of 4 or more was considered suggestive of the presence of clinically significant depression.[19] The MBI represented a cumulative score calculated by summing each item score, and the scores were multiples of 5, with a range of 0 (completely dependent) to 100 (independent).[20] An MBI score less than maximum (<100) indicated clinically significant difficulties in ADL.[21]

Statistical analyses were performed using *t* tests for normally distributed variables, while multiple group tests employed analysis of variance (ANOVA) and post-hoc testing. Kruskal-Wallis tests were used for nonparametric variables (eg, MMSE, SLUMS, EBAS-DEP, and MBI scores). Associations among these variables were determined using correlational analyses with Spearman's ρ. Significance was set at $P < .05$.

Table 1. *Subject Characteristics (Fasting)*

	CON	DM
N (M/F)	71 (25/46)	74 (24/50)
Age, y	55.5 ± 1.0	57.5 ± 1.3
Glucose, mg/dL	90.3 ± 1.1	132.1 ± 6.0*
Insulin, μIU/mL	8.3 ± 0.7	17.8 ± 2.1*
HbA1c, %	5.2 ± 0.0	6.6 ± 0.2*
Insulin resistance (HOMA)	2.3 ± 0.2	6.3 ± 0.8*
Total cholesterol, mg/dL	5.15 ± 0.08	4.69 ± 0.11*
HDL-cholesterol, mg/dL	1.40 ± 0.05	1.18 ± 0.04*
LDL-cholesterol, mg/dL	3.25 ± 0.07	2.81 ± 0.10*
Triglycerides, mg/dL	1.27 ± 0.07	1.55 ± 0.08*

* $P < .01$.

Table 2. *Physical Activity and Exercise Patterns*

	CON	DM
Regular exerciser, %	71.8	55.4*
Days of exercise/week, #	2.2 ± 0.3	2.2 ± 0.3
City blocks walked/day, #	20.3 ± 2.4	11.2 ± 1.5†
Stairs climbed/day, # flights	7.6 ± 0.8	3.5 ± 0.6†
Usual walking pace, 1–4	2.5 ± 0.1	2.0 ± 0.1†
Usual exertion, 0–10	4.3 ± 0.2	3.9 ± 0.2
Weekday, hours/day		
Vigorous activity	0.8 ± 0.1	0.8 ± 0.2
Moderate activity	3.2 ± 0.4	3.0 ± 0.3
Light activity	6.9 ± 0.3	5.5 ± 0.4†
Sit activity	5.4 ± 0.4	7.1 ± 0.5†
Sleep/recline activity	7.6 ± 0.2	7.6 ± 0.2
Weekend (hours/day)		
Vigorous activity	1.2 ± 0.2	1.0 ± 0.2
Moderate activity	4.2 ± 0.3	3.2 ± 0.3*
Light activity	5.4 ± 0.3	4.5 ± 0.3*
Sit activity	5.3 ± 0.4	7.1 ± 0.4†
Sleep/recline activity	7.9 ± 0.2	8.2 ± 0.2

* $P < .05$.
† $P < .01$.

RESULTS

The characteristics of the subjects are listed in Table 1. As expected, the DM group had higher blood glucose and insulin levels, as well as elevated HbA_{1c}. The groups differed by physical activity and exercise patterns (Table 2), with a greater percentage of CON subjects (71.8%) classified as "regular exercisers" compared with DM (55.4%; $P < .01$). CON subjects also walked significantly more city blocks per day, climbed more flights of stairs, and differed from DM in activity levels on weekday and weekends.

The results of mental function, depression, and self-care testing are shown in Table 3. On the MMSE, scores of 26 to 30 indicated "uncertain cognitive impairment," while those in the range of 22 to 25 were considered "mild to moderate cognitive impairment." For the DM group, 5 subjects (6.8%) scored between 22 and 25, while only 1 CON subject (1.4%) did. Thus, the majority of subjects recruited were unlikely to be suffering from an easily identifiable cognitive impairment

Table 3. *Mental Status and Other Measures*

	CON	DM
MMSE	29.3 ± 0.1	28.7 ± 0.2†
SLUMS	26.3 ± 0.8	25.7 ± 0.6
EBAS-DEP	1.6 ± 0.2	2.6 ± 0.3†
MBI	100.0 ± 0.0	99.1 ± 0.4*

MMSE, Mini-Mental Status Examination; SLUMS, Saint Louis University Mental Status Exam; EBAS-DEP, Even Briefer Assessment Scale for Depression; MBI, Modified Barthel Index.
* $P < .05$.
† $P < .01$.

detected by MMSE scores. When further subdividing groups by both diabetes and exercise statuses, the effect of regular physical activity was not significant ($P = .09$).

The SLUMS results are scored differently for individuals with less than a high school education, but this category applied to only 1 subject tested (CON). Scores from 27 to 30 indicated "normal" function, 20 to 26 showed "mild cognitive impairment" (MCI), and 19 or lower were interpreted as "dementia." SLUMS scores were not significantly different by group (Table 3), and almost equal numbers of CON and DM subjects fell into the range of MCI (31 and 29, respectively); however, 5 DM subjects (6.8%) scored 19 or less, while only 2 CON subjects (2.8%) were classified as demented. Further subdivision of scores by both exercise and diabetes statuses did not reveal any differences among groups.

On the EBAS-DEP scale, a score of "3" or greater was used to indicate the probable presence of a depressive disorder possibly needing treatment. A higher percentage of DM subjects (35.1%) scored a "3" or above on this scale compared with CON (12.7%; $P < .01$). When subdivided by both diabetes and exercise status, the scores for the CON exercisers indicated significantly less depression than for CON sedentary, DM exerciser, or DM sedentary subjects ($P < .01$). Mean depression scores were second lowest in DM exercisers (after CON exercisers), but not significantly lower than both sedentary groups.

All subjects for this study except for 1 wheelchair-bound DM participant were ambulatory, and very few ended up exhibiting more than minimal (score of 91 to 99) or mild (score of 75 to 90) impairment in their ability to do ADL as measured by the MBI, for which a maximal score of 100 indicated no impairment. All control subjects scored "100" on this test, while 8 DM subjects (11%) scored in the 80 to 95 range. The mean for DM subjects was significantly lower, as shown in Table 3 ($P < .05$). With groups further subdivided by exercise status, the DM sedentary group was significantly more impaired ($P < .01$) than all other groups.

Table 4 lists the associations among cognitive function, physical activity, and metabolic measures. Of note, MMSE and SLUMS scores were both positively associated with a greater duration of weekday light exercise, and depressions scores were associated with longer durations of sitting, which was also associated with higher fasting blood glucose levels. Age was inversely associated with MMSE scores, as were many of the metabolic parameters related to diabetes (ie, fasting insulin and IR). SLUMS scores were inversely associated with weekend sitting only, but positively related to moderate-intensity exercise on weekends. Depression scores showed an inverse association with a number of physical activity measures.

DISCUSSION

The primary goal of this study was to determine whether regular exercisers have a better cognitive status compared with nonexercisers and, more importantly, if subjects with diabetes who are regular exercisers have better cognitive function than sedentary diabetic (and even possibly control) sub-

Table 4. *Associations among Cognitive Function and Other Measures*

	P	*P* Value
MMSE (Cognitive Function)		
and weekday light exercise, hours	0.18	.04
and age	−0.31	<.01
and HOMA-IR	−0.19	.02
and insulin, μIU/mL	−0.18	.03
and SLUMS	0.22	<.01
SLUMS (Cognitive Function)		
and weekday light exercise, hours	0.17	.04
and weekend moderate exercise, hours	0.21	<.01
and weekend sitting, hours	−0.20	.02
EBAS-DEP (Depression)		
and weekday sitting, hours	0.18	.04
and weekend sitting, hours	0.16	.056
and HOMA-IR	0.17	.04
and weekend vigorous activity, hours	−0.26	<.01
and weekend moderate activity, hours	−0.18	.03
and # days/week of exercise	−0.19	.03
and daily stairs, # flights	−0.25	<.01
and daily blocks walked, #	−0.26	<.01
and MBI (self-care)	−0.25	<.01
MBI (Self-Care)		
and walking pace	0.29	<.01
and daily blocks walked, #	0.25	<.01
and daily stairs, # flights	0.27	<.01
Daily stairs, # flights		
and HOMA-IR	−0.40	<.01
and HbA1c, %	−0.30	<.01
# Days/week of exercise		
and exertion level	0.35	<.01
and weekday vigorous	0.51	<.01
and weekend vigorous	0.35	<.01
Walking pace		
and # days/week of exercise	0.49	<.01
and daily blocks walked, #	0.46	<.01
and HOMA-IR	−0.27	<.01
Fasting glucose, mM		
and weekend sitting, hours	0.27	<.01
and weekday sitting, hours	0.19	.03
and weekday light, hours	−0.17	.04
Fasting insulin, μIU/mL		
and weekday vigorous	−0.23	<.01
and weekend vigorous	−0.33	<.01

MMSE, Mini-Mental Status Examination; SLUMS, Saint Louis University Mental Status Exam; EBAS-DEP, Even Briefer Assessment Scale for Depression; MBI, Modified Barthel Index.

jects. The results demonstrated that diabetes has a negative impact on cognitive function measured with one measure of cognitive function, the MMSE, even when it is fairly intact in the groups being studied. Although "regular exerciser" status per se was not indicative of higher cognitive function, MMSE and SLUMS scores were significantly associated with specific physical activity measures, including a positive association with hours spent doing light exercise (like office work, driving, standing, and ADL) during the week and moderate weekend exercise and an inverse association with weekend sitting.

Depression may be a limiting factor for physical activity participation.[22] Individuals with diabetes are twice as likely to suffer from mild to moderate depression compared with their nondiabetic counterparts, and this condition, particularly when moderate or severe, has long been recognized as a limiting factor to regular exercise participation and self-care.[23] In that respect, the results of this study support prior findings. A lower percentage of DM subjects participated in regular exercise, and significantly more of them had depressive symptoms compared with nondiabetic participants. Physically active controls in this study were the least depressed group, and depression scores were inversely associated with a large number of physical activity variables. The DM group as a whole also walked fewer city blocks and stairs daily, had a slower walking pace, and spent less time doing light activities and more time sitting.

The presence of depression also makes the measures of cognitive function potentially more difficult to interpret and may have been a confounding variable in the present study. While depression appears to be more common in vascular dementia than in cases of AD,[24] it is still fairly prevalent in both diseases and may interfere with the diagnosis of cognitive impairment. In fact, even IR has been positively correlated to the severity of depressive symptoms, particularly in people with impaired glucose tolerance.[25] In the present study, measures of IR were higher in DM subjects and also were inversely associated with MMSE scores and directly related to depressive symptoms.

Other researchers have found that diabetes increases risk of dementias.[2–4] In one prospective study of 6370 elderly subjects, the presence of diabetes alone almost doubled their risk of dementia and AD, and those treated with insulin were at highest risk of dementia.[2] Poor cognitive function has also been associated with lesser control of blood glucose levels,[3] and working memory may be improved with enhanced diabetes control.[4] IR may contribute to cognitive impairment through a vascular mechanism,[26,27] and diabetes itself confers a greatly exaggerated risk of vascular complications.[28] A state of IR by itself has also been independently associated with lesser frontal cortex function as evidenced by poor Trail Making Test (TMT) times in older individuals without diabetes or dementia.[29]

Similarly, in a group of elderly Japanese men with diagnosed type 2 diabetes, poor cognitive function was evident, again more so in those individuals using insulin treatment.[3] Another study demonstrated that a cognitive benefit is achievable in reasonably well-controlled type 2 diabetic adults (mean age of 60 years; glycated hemoglobin levels less than 8.0%) with no evidence of dementia (using the MMSE) or depression, who further improve their blood glucose control through use of diabetic medications (ie, insulin sensitizers).[4] For those subjects, treatment-induced reductions in fasting plasma glucose levels were accompanied by improvements in cognition (ie, working memory).

Alternately, participation in any type of exercise may provide physiological benefits to diabetic individuals. For instance, acute improvements in insulin action in women with type 2 diabetes have been found whether they engaged in low-intensity or high-intensity walking as long as the total exercise energy expenditure was equivalent,[8] and even resistance training has been shown to improve it by 48% after 4 to 6 weeks of moderate resistance training.[7] In the present study, a lower state of IR was inversely associated with a faster walking pace, and fasting insulin levels were lower in individuals who participated in more vigorous activities.

Finally, it appears that physical activity also has the ability to decrease the risk of cognitive declines from the development of dementia or AD. In one study, participation in leisure activities was associated with a reduced risk of dementia, even after adjustment for baseline cognitive status and after the exclusion of subjects with possible preclinical dementia.[9] A meta-analysis of randomized clinical trials from 1970 to 2003 also concluded that exercise training increases not only fitness and physical function, but also cognitive function and positive behavior in people with dementia and related cognitive impairments.[30]

Moreover, a prospective study of rural elderly people (n = 1146, ages 65 years or more) that examined self-reported exercise habits and measured cognitive function with the MMSE found that all levels of exercise participation were negatively associated with cognitive decline over a 2-year interval.[10] Likewise, in 1740 individuals over the age of 65 years who were followed biennially for more than 6 years, regular exercise was associated with a delay in the onset of dementia and AD.[11] Although others have recently concluded that intensity is more important than duration as far as cognitive function is concerned,[31] even in elderly men, participation in physical activities with at least a medium-low intensity may postpone cognitive decline, and maintenance of both exercise duration and intensity over time is important.[32] The findings of the current study are in accordance with these latter findings given that both light activity during the week and moderate exercise on weekend days were associated with better cognitive function.

An obvious confounding variable in the interpretation of cognitive function, depression, and self-care measures in this study was that all enrolled subjects were capable of answering the questions without assistance. As a result, the minimum score (out of 30 possible) was 23 for the MMSE and 16 for the SLUMS. However, although not many severely cognitively impaired individuals participated, the 2 groups differed significantly on MMSE scores by diabetes status. One explanation of the selection of the participants is that since all subjects had to report to the laboratory on campus on their own for testing, fewer cognitively impaired individuals volunteered to participate or showed up for testing. Had subjects been recruited from assisted-living facilities instead, likely a greater cognitive impairment in subjects would have been evident.

CONCLUSION

Certain types of physical activity appear to be beneficial in the maintenance of cognitive function given that both MMSE and SLUMS scores were positively associated with a greater duration of weekday light exercise and SLUMS scores correlated with longer moderate exercise on weekends. Longer weekend sitting also was associated with higher blood glucose levels and greater depression, and a number of physical activity behaviors were inversely associated with depression, which by itself is a risk factor for reduced time spent engaging in physical activity. Similarly, having diabetes, particularly when less well controlled, appears to be a significant risk factor for lower cognitive function scores on some tests, and certain types of physical activity participation may prevent some of the potential decline in cognition.

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