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Research Article

Type 2 Diabetes, Physical Activity and Risk of Mild Cognitive Impairment and Dementia in Community Dwelling Old Adults

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Abstract

Introduction: We aim to investigate the longitudinal associations between level of physical activity (PA) and the risk of mild cognitive impairment (MCI) and dementia among type 2 diabetes (T2D) and pre-diabetes (PD) participants who are cognitively normal at study entry.

Methods: We used data from the Age-Gene/Environment-Susceptibility-Reykjavik-Study (65-96 years). From the original sample, 3001 participants with a complete evaluation of T2D, MCI and dementia were included in this analysis.

Results: During follow-up (5.2 years), 8.5% (n = 256) developed MCI and 3.7% (n = 111) developed dementia. T2D participants had an increased risk for MCI (OR = 1.632, P = 0.021) and both PD and T2D individuals had increased risk for dementia (OR = 1.947, P = 0.003 and OR=2.101, P = 0.026). PA was associated with lower dementia risk in normal participants only (OR = 0.611, P = 0.019).

Discussion: Older adults with PD/T2D had low level of PA and higher risk of declining cognitive function.

Keywords: Type 2 Diabetes; Mild Cognitive Impairment; Dementia; Physical Activity; Glucose Regulations

Introduction

Diabetes has been increasing worldwide [1] with increasing prevalence associated with age, making older adults frequently affected [2]. Type 2 diabetes (T2D) accounts for the majority of diabetes patients (85% to 90%), characterized by a worsening insulin sensitivity finally resulting into hyperglycemia [3] being a serious cause of cardiovascular disease, kidney disease and neuropathy [4]. Studies have suggested that old adults with T2D have a higher risk (>50%) for developing cognitive deficits, especially when glycemic control is poor [5-7].

Regular physical activity (PA) can have positive effects for glucose regulations especially in patients with T2D [8,9], and recent studies have indicated that PA can improve cognition in old adults as well [10,11]. Epidemiological studies often associated physical exercise with improved cognitive function [6], decreased hazards

of dementia and fewer ageing associated alterations in the brain [12,13]. Data from brain imaging studies indicate that physical activity can prevent brain atrophy in old populations and experimental evidence suggests that resistance training also positively effects cognition in this age group [14,15]. Additionally, PA can improve glucose regulations and cardiovascular risk factors which all represent a threat for good cognitive function when compromised [16-18].

Despite that the evidence is solid that PA is related to good cognitive function, majority of research has been carried out in healthy older adults. Current literature is less clear whether the positive findings on PA and cognitive function can be applied to old adults with poor glucose regulations or diabetes [19]. A recently published systematic review investigating the relationship between exercise and cognitive function in participants with diabetes or poor glucose regulations were only few of the cognitive outcomes were significant [16].

Thus, the present cohort study investigated T2D, PA and risk of MCI and dementia during 5.2 years of follow-up in community dwelling old Icelandic adults.

The specific aims of the present study were to investigate: the MCI- and dementia risk in healthy, pre-diabetic and diabetic participants; whether lower PA and poorer lifestyle in diabetic participants explain increased risk of MCI or dementia; whether diabetic status modifies the ability of PA to prevent MCI or dementia.

Methods

Study population and study design

This longitudinal analysis is based on data from the AGES-Reykjavik study (N = 5764) enrolled in 2002-2006 as a continuation of the population-based Reykjavik Study (RS) in Iceland, initiated in 1967. Detailed baseline information have been described in a previous AGES-study paper [20]. Between 2007-2011, AGES I participants (58%, N = 3316) returned to a second examination, a 5-year follow-up visit (AGES II). The current study included participants who were cognitively normal at baseline examination and had the relevant follow-up examination including a cognitive test battery (N = 3001). The study was approved by the National Bioethics Committee in Iceland (approval VSN-00-063), the Data Protection Authority and by the National Institute on Aging Intramural Institutional Review Board. Written informed consent was obtained from all participants.

Anthropometrics

Weight and height were measured and BMI was calculated as kg/m^2.

Mild cognitive impairment and Dementia

The criterion for MCI diagnosis was having deficits in memory or one other domain of cognitive function or deficits in at least 2 cognitive domains without being severe enough to cross the threshold for dementia and without loss of instrumental activities of daily living [21].

Assessment of dementia was done following a three-step protocol and according to international guidelines from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [22]. First, the digit symbol substitution test (DSST) [23] and the Mini-Mental State Examination (MMSE) [24] were administered to the total sample. Participants who scored 23 or lower on the MMSE or had a raw score of 17 or lower on the DSST were administered a second diagnostic cognitive test battery. Participants who scored 8 or more on Trails B [25] (ratio of time taken for "Trails B/Trails A") or had lower than total score of 19 for the four immediate recall trials of the Rey Auditory Verbal Learning [26] went on to a third step. This step included a neurological test and a proxy interview regarding medical history, social, cognitive, and daily functioning changes of the participant.

Diabetes mellitus and pre-diabetes

Participants were categorized into being type 2 diabetic (diagnosed either as fasting serum glucose of ≥ 126 mg/dL, self-reported diabetes and/or use of diabetes medication), pre-diabetic (fasting blood glucose ≥100 to <126 mg/dL) [27] and normal health (neither of above definitions).

Covariates

Demographic and lifestyle data

Participants were asked about their age, gender, smoking habits (current smoking yes or no), alcohol consumption (shown as g/week). Physical activity was assessed by a self-reported questionnaire. Participants were asked, how many hours per week they participated in moderate intensity PA in the past 12 months. Predefined answer categories were never, rarely, weekly but <1 hour

per week, 1-3 hours per week, 4-7 hours per week and more than 7 hours per week. In statistical analyses PA categories were combined (≤ 3 h vs. > 3 h). Education was categorized into two levels (elementary school or high school vs. undergraduate or more than undergraduate education). Participants were instructed in advance to bring all medication they had used during the preceding two weeks before the clinic visit.

Laboratory data

The accredited IHA laboratory performed 25OHD measurements using unfrozen serum samples and the Liaison chemiluminescence immunoassay (DiaSorin Inc, Stillwater, Minnesota). Existing serum 25OHD levels were then standardized [28]. Glucose levels in a capillary blood sample were estimated by the Hoffman ferricyanide method, adapted to the Technicon-Method N-9a [29,30]. Glucose was measured on a Hitachi 912, using reagents from Roche Diagnostics following the manufacturer's instructions. Insulin was measured with a Roche Elecsys 2010 instrument [31].

Apolipoprotein E genotype

The final sample in current study were all genotyped for APOE ε4 alleles using standard methods [32]. Participants were considered APOE ε4 positive if they carried ε3/4, and ε4/4 genotype otherwise if they carried ε2/2, ε2/3 and ε3/3 they were considered APOE ε4 non-carriers.

Statistical analysis

Statistical analyses were carried out using IBM SPSS version 26.0 (SPSS, Chicago, IL, USA). Baseline characteristics of the participants categorized by diabetic status are shown in table 1. We used chi-square test for categorical variables and after visual inspection of the distribution and calculation of variances, we used ANOVA or Kruskal Wallis test for continuous variables to test for statistical differences. As distributions were not normal and variances between the three categories of participants were not similar for alcohol, number of medicines, glucose and insulin, we used Kruskal Wallis test.

To calculate whether diabetes status predicts onset of MCI or dementia (Table 2) logistic regression analyses were applied controlling for various confounders. For each outcome variable the following 3-step model was applied: Model 1 adjusted for age and gender; model 2 additionally adjusted for smoking, education and BMI; model 3 additionally adjusted for 25OHD, PA and APOE ε4.

	Normal	Pre-diabetic	Diabetic	
	(n = 1570)	(n = 1124)	(n = 307)	
	Mean ± SD	Mean ± SD	Mean ± SD	P-value*
Age (years)	75.3 ± 4.9	74.6 ± 4.9	75.1 ± 4.6	<0.001
Women (in %)	64.5	53.0	46.7	<0.001
Smoking (yes in%)	9.1	7.8	6.6	0.218
Higher education (in %)	28.4	27.2	29.0	0.721
Alcohol (g/week)	14.7 ± 31.7	18.7 ± 37.6	15.4 ± 35.3	0.040
Number of medications**	3.5 ± 2.7	3.5 ± 2.6	5.5 ± 3.0	<0.001
BMI (kg/m^2)	26.3 ± 4.0	28.1 ± 4.2	29.1 ± 4.5	<0.001
Obese (yes in %)	16.5	29.5	39.8	<0.001
Physical activity (no in %)	35.2	32.2	28.2	0.011
Physical actvity > 3h/week (%)	58.9 ± 17.3	58.1 ± 17.8	55.0 ± 16.7	<0.001
25OHD (nmol/L)	93.0 ± 5.0	107.4 ± 6.0	140.5 ± 35.9	<0.001
Glucose (mg/dL)**	8.5 ± 5.6	13.8 ± 7.5	15.3 ± 9.4	0.214
Insulin (mU/L)**	27.3 ± 2.5	27.2 ± 2.4	27.1 ± 2.6	0.028
MMSE (baseline score)	8.5	8.2	13.1	0.040
MCI during follow-up† (%)	3.2	4.7	5.9	
Dementia during follow-up (%)				

Table 1: Characteristics of AGES-Reykjavik participants according to diabetic status.

Abbreviations: BMI: Body Mass Index; 25OHD: 25 hydroxyvitamin D; MMSE: Mini-Mental State Exam; MCI: Mild Cognitive Impairment.

*Based on chi-square test for categorical variables and ANOVA for continuous variables. P-values for alcohol, number of medicines, glucose and insulin are based on Kruskal Wallis test.

†Mean follow-up time 5.2 years.

		MCI development				Dementia development			
		(n = 2890)				(n = 2745)			
		OR	95% CI		P-value	OR	95% CI		P-value
Model 1	Normal	1.000			Ref.	1.000			Ref.
	Pre-diabetic	1.026	0.766	1.375	0.862	1.735	1.137	2.647	0.011
	Diabetic	1.696	1.139	2.528	0.009	2.224	1.219	4.060	0.009
Model 2	Normal	1.000			Ref.	1.000			Ref.
	Pre-diabetic	0.954	0.704	1.293	0.763	1.911	1.236	2.957	0.004
	Diabetic	1.594	1.054	2.412	0.027	2.543	1.37	4.718	0.003
Model 3	Normal	1.000			Ref.	1.000			Ref.
	Pre-diabetic	0.962	0.71	1.304	0.805	1.913	1.235	2.961	0.004
	Diabetic	1.584	1.044	2.403	0.031	2.43	1.304	4.529	0.005

Table 2: Risk* of MCI and dementia during follow-up in normal, pre-diabetic and diabetic participants.

Abbreviations: MCI: Mild Cognitive Impairment; OR: Odds Ratio; CI: Confidence Interval.

*Based on logistic regression

Model 1: Corrected for age and gender

Model 2: Additionally, corrected for BMI, smoking and education.

Model 3: Additionally, corrected for physical activity, 25OHD and APOE ε4.

To calculate whether the risk of MCI or dementia diagnosis can be minimized among diabetic participants through physical activity, data were stratified by diabetic status and then logistic regression models were used. The outcome variables were MCI and dementia; the main independent variable was PA. In model 1 we adjusted for sex; in model 2 we additionally adjusted for age (Table 3).

The level of statistical significance was set at $p < 0.05$.

Results

The characteristics of the participants categorized by diabetic status are shown in table 1. Participants with diabetes were more often men, had higher baseline BMI, lower vitamin D levels, used more medication and were less physical active. Education, smoking and MMSE were not significantly different between the categories.

Of 3001 participants, 256 (8.5%) developed MCI and 111 (3.7%) developed dementia during a mean follow-up of 5.2 years. Tables 2 shows the results from logistic regression models estimating the MCI- and dementia risk for pre-diabetic and diabetic participants compared to normal participants. The calculations show an increased MCI risk for diabetic participants which was largely independent from lifestyle associated covariates or education. We also found an increased risk for dementia in both pre-diabetic and diabetic individuals when compared to normal individuals, in fully adjusted model.

The effect of the interaction between physical activity and diabetes on cognitive function outcome was not significant ($P_{interaction} > 0.05$ for all, supplementary table 1). Table 3 shows the associations between PA and MCI/dementia risk stratified by diabetes status and adjusted for gender. Physical activity at baseline was associated with lower MCI risk during follow-up in normal and pre-diabetic (borderline) participants only, but not in diabetic (model 1). Part of this association was driven by age and corresponding adjustment weakened the statistical significance (model 2).

Physical activity was also associated with lower dementia risk in normal participants only, but not in pre-diabetic and diabetic participant (table 3, model 1). Here also, part of this association was driven by age and statistical significance disappeared after corresponding statistical adjustment (table 3, model 2).

Discussion

In this cohort study diabetic participants had higher MCI and dementia risk during five years of follow-up, and pre-diabetic subjects had higher dementia risk, when compared to subjects with normal glucose metabolism at baseline. Our study suggests that lower PA in diabetic participants did not explain their increased risk of MCI or dementia. The results indicate that PA was protective for MCI- and dementia risk in normal, but neither in pre-diabetic nor in diabetic participants.

			MCI development				Dementia development			
			(n = 2890)				(n = 2745)			
	Stratification	Independent variable	OR	95% CI		P-value	OR	95% CI		P-value
Model 1	Normal	physical activity †	0.499	0.347	0.718	<0.001	0.553	0.306	0.997	0.049
	Pre-diabetic	physical activity	0.658	0.424	1.021	0.062	0.664	0.373	1.183	0.165
	Diabetic	physical activity	0.999	0.502	1.987	0.996	0.825	0.300	2.270	0.702
Model 2	Normal	physical activity	0.611	0.420	0.891	0.019	0.737	0.401	1.353	0.399
	Pre-diabetic	physical activity	0.832	0.527	1.314	0.441	0.864	0.475	1.573	0.633
	Diabetic	physical activity	1.145	0.558	2.348	0.717	0.878	0.314	2.456	0.749

Table 3: Risk* of MCI and dementia in normal, pre-diabetic and diabetic participants depending on physical activity.

Abbreviations: MCI: Mild Cognitive Impairment; OR: Odds Ratio; CI: Confidence Interval.

*Based on stratified logistic regression

†as compared to no physical activity

Model 1: Corrected for gender

Model 2: Corrected for gender and age

		MCI development				Dementia development			
	Interaction	OR	95% CI		P-value	OR	95% CI		P-value
Model 1	Physical activity*Diabetic status	0.991	0.865	1.134	0.892	1.021	0.834	1.249	0.843
Model 2	Physical activity*Diabetic status	0.981	0.856	1.124	0.781	0.992	0.811	1.212	0.936

Supplementary Table 1: Interaction† between physical activity and diabetic status.

Abbreviations: MCI: Mild Cognitive Impairment; OR: Odds Ratio; CI: Confidence Interval.

†Based on logistic regression

Model 1: Corrected for gender.

Model 2: Corrected for gender and age.

Disturbed glucose levels have been associated with an elevated risk of poor cognitive function as well as dementia when compared to healthy subjects [33,34]. According to meta-analyses [35,36] the risk for dementia diagnosis is increased by 51-73% in diabetics and our own results show somewhat higher odds between +110 to 147% depending on the degree of statistical correction. Furthermore, studies also show an increased risk for MCI in diabetic subjects (+21%) [35] which is slightly lower than observed in our study.

There are only few studies available in literature investigating the effects of PA on cognition in participants with diabetes or disturbed glucose regulations and none of these studies have shown reduced risk from PA [19,37-41]. There are several possible explanations why PA has not been found beneficial in the prevention of

dementia in previous studies. Some cohorts consist of rather young subjects, still showing good cognitive performance at the end of the research and in intervention studies the follow-up time might be too short to produce meaningful changes in cognition.

In the present observational study, PA levels were generally low with the lowest proportion among T2D subjects and PA was categorized into "≤ 3 h" vs." > 3 h". Although a more detailed categorization of PA was possible in our data, too few cases of dementia and MCI were in the single categories undermining meaningful statistical analysis. It is therefore interesting to speculate whether a higher level of PA in conjunction with a good glycemic control is necessary to maintain cognition during ageing.

In contrast to the currently available weak evidence of PA and the prevention of cognitive decline in individuals with disturbed glucose regulations, it should be mentioned that studies have shown that increased physical activity has clear beneficial physiological and psychological effects for older adults with T2D [42].

Limitation

Results of this study may be limited since categorization of major subtypes of dementia such as vascular dementia were not available and participation in PA among T2D participants might have been too low to detect the protective levels of PA.

It is a further limitation of this study that we used physical activity as a dichotomous variable which lead to a loss of information. Available data on physical activity were based on predefined answer categories beyond our control: never, rarely, weekly but <1 hour per week, 1-3 hours per week, 4-7 hours per week and more than 7 hours per week. PA categories were the further combined (≤ 3 h vs. > 3 h) for statistical reasons as very few participants were physical active > 7 hours/week.

Conclusion

Our study showed that that community dwelling old adults with T2D had higher dementia and MCI risk during follow-up and pre-diabetic subjects had higher dementia risk, when compared to community dwelling old adults with normal glucose levels. In contrast to our expectations, PA was not protective from MCI and dementia neither in pre-diabetic nor in type 2 diabetic participants.

Conflict of Interest

The authors declare no conflict of interest.

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