IJAHS-0137

PHYSICAL ACTIVITY AND COGNITIVE DYSFUNCTION ASSOCIATED WITH TYPE 2 DIABETES MELLITUS: A REVIEW ARTICLE.

Raana Ali Mirza, MSNMPT: Department of Rehabilitation Sciences, University of Lahore, Islamabad.
Irum Yaqoob, MSNMPT: Riphah college of Rehabilitation Sciences, Riphah International University, Islamabad.

Date of Received: 21/03/2018 **Date of Acceptance:** 14/05/2018

ABSTRACT

Background: Type 2 diabetes mellitus along with its associated factors like insulin resistance and hyperglycemia is found to impair the certain domains of cognition e.g. executive functions and verbal ability. Many of these functions can be modified through regular physical activity, hence can improve cognition. **Purpose:** The purpose of this article was to link the available literature related to impacts of physical activity on the diabetes associated cognitive dysfunction. **Methods:** The available literature discusses the effects of different exercise protocols on several factors linked to diabetes and its effects on cognitive function. Literature search was conducted for the articles in last twelve years using different online databases (Pub Med, Google scholar) and All experimental or non-experimental studies relevant to the effects of exercise or physical activity cognitive function on Type 2 diabetes mellitus (T2DM). **Conclusion:** On the basis of the available evidences we can conclude that physical activity can alter the factors associated with diabetes that result in the development of cognitive dysfunction. Hence exercise can improve cognitive status as well as other markers of Type 2 diabetes.

Key words: Cognitive dysfunction, Physical activity, Type 2 Diabetes mellitus.

Correspondence Address
Irum Yaqoob
MSNMPT:
Riphah college of Rehabilitation Sciences,
Riphah International University,
Islamabad.
irum.yaqoob@riphah.edu.pk

Article Citation: Mirza AR, Yaqoob I. Physical Activity And Cognitive Dysfunction Associated With Type 2 Diabetes Mellitus: A Review Article. **IJAHS,** Apr-Jun 2018;02(04-06):81-89.

INTRODUCTION

According to the American Diabetes Association, diabetes being metabolic disorder is characterized by reduced insulin due to either its reduced production or insulin resistance resulting in hyperglycemia.[1] There are two common types of DM, type 1 and type 2. Type 2 diabetes mellitus (T2DM) is observed in adults and it represents 90-95% cases of Diabetes[1,2].

There are certain factors that are associated with DM i.e. smoking, obesity and weight gain are modifiable risk factors of diabetes. Cessation of smoking along with control of weight can decrease the risk of developing diabetes.[3,4] Exercise along with dietary modifications, pharmacological interventions and modification of other risk factors is considered a keystone in order to manage DM.[1,5]

Prevalence of diabetes in adult population worldwide is estimated to be 285 million, and it is expected that this number will rise up and will have deleterious effects on the health as well as quality of life (QOL).[5] Evidence shows that diabetes type 2 increase the risk of cognitive impairments that can present in up to 80% of individuals with dementia over the age of 65 years or older.[6] Literature also reveals that healthy life style can decrease the odds of developing dementia.[7]

This article was aimed to highlight the beneficial effects of physical activity that impact the factors like insulin resistance, hyperglycemia and their association with cognitive function among diabetics. References in this article were retrieved via Pub Med search using keywords like" Diabetes," "Type 2 diabetes," "cognitive decline," "cognitive dysfunction," "exercise intervention," "exercise training," "dementia" and "Alzheimer's disease.". Allthose studies were included if they met the inclusion criteria that is as follows: 1) randomized control trial (RCT), non-randomized controlled trial (NRCT), or observational study 2) Full-length article published in a peer-reviewed journal. 3) All studies including only human subjects diagnosed with T2DM or impaired glucose intolerance following any kind of physical activity based interventions. Searching of the databases and literature review was done in duration of 3 months. The compilation and writing of the manuscript was done in 4 months' duration.

Diabetes mellitus and cognitive dysfunction

Evidences on diabetes shows diabetics are at increased risk for the development of cognitive impairments.[8,9] According to a review mild to moderate cognitive declines were observed among diabetics. Reduced performances were documented in multiple cognitive domains including episodic memory, information processing speeds and task executive functioning.[10,11] A 15-year follow-up study on diabetes reported that co-morbidities associated with diabetes affect the nervous system causing diabetic encephalopathy, resulting in the neuronal damage and consequently losing them hence contributing to cognitive dysfunction.[12] The factors like the end organ damage influenced by hyperglycemia, vascular and neuronal damage, hypoglycemia and the presence of amyloid lesions may be held responsible for the changes and damages to cerebral structure.[9] Cognitive dysfunction is also related with diabetic-comorbidities including increased obesity, low muscle mass, depression, cardiovascular diseases, chronic inflammation and cerebrovascular diseases.[8,13]

Several longitudinal studies suggest that there is a strong association between cognitive dysfunction among patients with T2DM which may even lead to dementia in severe cases.[14,16]

Fluctuating blood glucose levels and cognitive changes

Monitoring of blood glucose level regularly indicate that its fluctuations have direct impact on cognition.[17] Studies suggests that the alterations in blood glucose and hyperglycemia can elevate the oxidative stress hence induce vascular as well as neuronal damage as a result cause cognitive decline.[8] High levels of random blood glucose levels (BSR) also affect the cognitive ability of people having diabetes mellitus.[18] As high BSR contribute towards cognitive impairments studies also show that severe and recurrent episodes of hypoglycemia may contribute to cognitive dysfunction.[19] A longitudinal cohort study including 16,667 participants showed that among the older adults the high incidence of hypoglycemia was associated with higher rates of developing dementia and cognitive deficits.[19] Another prospective ACCORD trail in 2012 stated, among the patients with T2DM cognitive decline was highly related with increasing levels of hypoglycemic events.[20] A Meta-analysis/systematic review on hypoglycemia induced cognitive dysfunction identified hypoglycemia as being an important factor for the development of dementia among T2DM patients.[21]

Benefits of exercise in t2dm

Large number of studies demonstrate the benefits of exercise in improving cognition along with other diabetes related complications. The recommended guidelines for diabetics suggest that diabetics should perform minimum of 150 minutes/week moderate intensity aerobic training along with resistance training for 2-3 times/week.[22] Some of the studies related to the impact of exercise on diabetics are discussed below.

Exercise on cognition

Exercise promotes the production of IGF-1 from brain along with other neurotrophic factors which have rejuvenating effects on brain for enhancing cognitive abilities.[23]

It is well known that diabetes mellitus is found to be associated with many co-morbidities().Many studies have been done that shows the promising positive impacts of exercise and physical activity to improve cognition, glycemic control, body composition and physical functioning hence improve well-being.[25]

Below is the discussion on4 experimental and 2 cross sectional studies concerning the impact of exercise among diabetics.

A longitudinal study taking 145 (74 diabetics and 71 non-diabetic) participants was done in 2008 by Colberg and colleagues. The participants were assessed through different cognition scales such as Mini-mental State Examination (MMSE), Saint Louis University Mental Status exam (SLUMS), the Even Briefer Assessment Scale for Depression (EBA-DEP), the Modified Barthel Index (MBI) and Harvard Alumni Physical Activity Questionnaire(HAPAQ) were assessed along with. Fasting insulin, insulin resistance, HBA1C, fasting blood glucose levels and lipid profile. Results showed 6.8% of Diabetics participated in the study had Mild cognitive impairment i.e. <25 score MMSE (22-25) while only 1.4% control participants had mild cognitive impairment according to MMSE ($p=0.01$). Several associations were found between lifestyle factors and cognitive performances. Scores on MMSE and SLUMS were positively correlated with the greater duration of weekday light exercise. SLUMS scores were also associated positively with moderate-intensity weekend exercise, while there was negative correlation of these test with increased sitting. At the end of study authors concluded that there are some exercises that improves the cognitive abilities of diabetics.[26] The study is summarized in table no.1.

Another cross-sectional study was done on association between physical activity and cognition among diabetic women. found no significant relation. For the purpose of this longitudinal study cognitive assessment of 1,550 nurses with T2DM and aged >70years was done. Different cognitive tools were used to assess the cognition including TICS, East Boston Memory Test, Digital-Span Backwards, Category Fluency. Distribution of these participants was done into 3 tertiles according to their levels of physical activity and thee value of metabolic equivalent (MET). Each physical activity was assigned METsof energy while considering 1 MET to be equivalent to the amount of energy expended while quite sitting. The initial baseline measurements were taken and the mean difference was taken in comparison to follow after measures in two years. Initially the results showed significant relation between physical activity and cognition. But after the adjustments of cofounders like physical disability the results were non-significant. Follow-up assessments were completed twice at 2-year intervals.[27] The summary of above mentioned study is described in table 2.

An RCT was conducted by Watson and colleagues in 2006 on Japanese American population having glucose intolerance and hyperinsulinemia. The researchers studied the

Table 1

Author/ Study type	Total number(n)/ m.a (mean age)	Tools/ Measures	Results					
			Cognitive measures			Other measures		
Colberg et al[26] 2008/ Cross-sectional	n=145 CON=71 DM=74 m.a=33.8	MMSE SLUMS EBA-DEP MBI FI FBS HBA1C lipids profile		DM	CON		DM	CON
			*MMSE	28.7±0.2	29.3±0.1	*Regular exercisers†	55.4	71.8
			SLUMS	25.7±0.6	26.3±0.8	*FI IU/mL	17.8±2.1	8.3±0.7
			*EBA-DEP	2.6±0.3	1.60±0.2	*FBS mg/dL	132.1±6.0	90.3±1.1
			MBI	99.1±0.4	100±0.0	*HBA1C	6.6±0.2	5.2±0.0
						*T.C mg/dL	4.69±0.11	5.15±0.08

*p= 0.01 / † regular exercisers (HAPAQ) = subjects engaging in at least 30 minutes of moderate aerobic exercise 3 times a week for a minimum of 1 year

Table 1 Summary of cross-sectional study on association between physical activity and cognition among T2DM.

Table 2

Author/ Study type	Total number(n)/	Tools/ Measures	Results				Conclusion
Devore et al 2009[27]/ Cross-sectional	n=1550 ♀ age >70y	TICS MMSE EBM DSB CF		Tertile 1 (n=512)	Tertile2 (n=520)	Tertile3 (n=518)	There was no Apparent association between physical activity and cognitive function after adjustment for indicators of physical disability.
			MET-hours (median)*	3.38	10.70	24.39	
			Baseline cognitive scores, mean (SD)				
			TICS	33.2 (2.6)	33.3 (2.8)	33.7 (2.8)	
			Global	-0.03(0.6)	-0.03 (0.6)	0.05 (0.6)	
			Verbal	-0.03 (0.7)	-0.04 (0.7)	0.05 (0.7)	

* 1 MET- hour is the amount of energy expended by sitting quietly for 1 hour

Table 2 Summary of cross-sectional study on association between P.A and cognition among T2DM women.

effect of diet and exercise on the participants. Study groups were either active or control i.e. control (n=13) and active (n=15). Baseline characteristics were similar in both groups including age, BMI, VO_{2max} and Oral glucose tolerance test (OGTT). Both groups followed different exercise and diet plans for 12 months, with baseline measures taken before exercise and follow up measures were taken at 6th and 12th month. Control group followed supervised plan of stretching for 1 hour, 3 days/ week for 6 months along with American Heart Association(AHA) step 1 eucaloric diet after that the participants followed same program at home unsupervised. Whereas the active group followed a supervised plan of walking/ jogging on treadmill for 1-hour duration 3days/week for 12 months. During the period of 12 weeks the effort was increased from 50-70% of heart rate reserve (HRR). AHA step 2 diet plan was followed by the participants enrolled in active group. Summary of intervention protocols is shown in table 3.The results (table 4) showed 6 months of training improved BMI and Vo_{2max} in both groups. The results showed performances in story recall test were associated with the changes in the value of intra-abdominal fat (IAF). The levels of retaining of information were improved in the active group and this improvement was not associated with the values of IAF. On the other hand, it was found that control group improvements in the domain of memory were associated with the loss of IAF. 2-h OGTT insulin levels were decreased among the active group and it was associated with improvements in delayed recall concerning story recall test and Benton visual retention test. It was concluded that exercise along with dietary modifications are important for improving metabolic parameters and verbal memory among diabetics.[28]

Another RCT was done in 2010 including 34 participants with mean age of 69.4, to evaluate the effects of aerobic exercises among T2DM with glucose intolerance. Participants were randomly recruited to aerobic group and control group and duration of training was 6 months. Aerobic group protocol included exercise training using treadmill or stationary cycle for 40-60mins/ session for 4 days/week. The intensity was maintained between 75-80% HRR. The control group followed stretching and balance exercises while maintaining the intensity of 50% HRR. Cognitive testing was done concerning the domains of executive functioning and memory. The tools used for executive function were trail making test A/B, Stroop color interface test, task switching, verbal fluency test, self-ordered pointing test and for memory included story recall and list learning. Other parameters included insulin sensitivity, body fat, and fasting plasma levels of insulin, cortisol, brain-derived neuro-trophic factor, insulin-like growth factor-1, amyloid-β (Aβ40 and Aβ42). (table 3). Results showed improvements in cardiorespiratory fitness (p=0.03) as measured by treadmill measures of VO2max. The glucose disposal was improved among the active aerobic group as compared to the control group. (p=0.05). A positive correlation was found among the improvements in glucose disposal and cardiorespiratory capacity. At the end of the trial, adiposity and plasma triglyceride levels decreased for both groups relative to baseline. While considering the Alzheimer's related biomarkers, the Plasma levels of $A\beta_{42}$ decreased for the aerobic group as compared to the control. Table 4 shows summary of the results of the study.

Regarding cognitive measurements, the results showed improvements in executive function (p=0.04). The active group showed improvements in Trail-B test (p=0.04), Task Switching (p=0.03) and Stroop test (p=0.04). In contrast with the study of Watson et al significant improvements were observed only in the domain of executive function as compared to the memory. Hence it was concluded that structured exercise programs may prove beneficial for improving the executive function among adults with T2DM. Furthermore physical activity improves the metabolic parameters and may have remediating effects on frontal lobe, improving cognitive abilities, by decreasing the Alzheimer's associated parameters like $A\beta_{42(0)}$.[29]

In 2011, Yanagawa et al evaluated the association between improvements in insulin resistance and cognitive function among T2DM patients. Summary of the study is shown in table 3 and 4.

16 participants with mean age of 70.9 years were recruited randomly to the control and exercise groups. The control group participants maintained their usual level of activity while exercise group was instructed to exercise 4 days per week for 12 weeks using horse riding simulation equipment. Minimental state examination, Trail-B, Word List (delayed memory) and Stroop test were used to assess the cognitive function. Other metabolic parameters including insulin sensitivity, plasma glucose levels and glucose infusion rates were also measured. Although no significant improvements were observed in cognitive function but a positive

Table 3

Author	Total number(n)/ Mean age(M.A)	Study type	Tools	Control Group	Active Group
Watson et al[28] 2006	n=28 a.g=15, c.g=13 M.A: a.g=58.0±9.7 c.g =60.6 ± 9.0	RCT	SR BVR TMT ST	C= 12m D= 1h F= 3d/wk I= NR T=stretching exercises +AHA step1 diet.	C= 12m D= 1h F= 3d/wk I= 50-70%HRR T= walking/treadmill+ AHA step2 diet
Baker et al[29] 2010	n=28 c.g=9/a.g=19 M.A=69.4	RCT	TMT A/B TS Stroop V.F SR SOPT	C=6m D= 45-60min F=4d/wk I=50%HRR T=stretching +balance exercises	C=6m D=45-60min F=4d/wk I=75-80%HRR T=walking, jogging via treadmill/stationary bicycle
Yanagawa et al[30] 2011	n=16 c.g=7/a.g=9 M.A=70.9±3.7	RCT	MMSE TMT-A/B WLIM/D Stroop	Maintained their usual levels of physical activity	C=12 wk D= 45min F=4d/wk I=<6METS T=horse riding simulation equipment.
Anderson-Hanley et al[31] 2012	n=10 M.A= 72.8	QES	CT Stroop-C DSBT	(Non-diabetics) C=3m D=45min F=5d/wk I=60-85% HRR T= cyber cycling/ stationary cycling	(diabetics) C=3m D=45min F=5d/wk I=60-85% HRR T= cyber cycling/ stationary cycling

Table 3 Summary of experimental studies on effects of exercise and cognitive function in T2DM

Table 3

Author	Results	Conclusion
Watson et al[28]	After 6 months: Vo2 max ↑(p= 0.04) BMI* improved (p = 0.013) 2-h OGTT IL reduced in A.G (p=0.02) <u>Cognitive measures</u> • SR* = A. G= ↑(p =0.01) C.G = ↑when IAF ↓(p =0.02) • BVR= N/R • TMT=N/R • ST=N/R	-Improved levels of metabolic parameters and verbal memory were associated with enduranc exerciseand dietary fat restriction. ↓Levels of insulin were associated with retaining of information observed in the aerobic group.
Baker et al[29]	↑Cardiorespiratory fitness(p=0.03) ↑Glucose disposal (p = 0.05) ↓adiposity, triglycerides ↓Aβ24 (p=0.07) <u>Cognitive measures:</u> ↑ executive functioning (p= 0.04) A.G showed improvement in TMT-B(p=0.04) TS(p=0.03) Stroop(p=0.04)	Aerobic exercises have remediating effects on frontal lobe, improving executive function and may help to reduce the risks of developing Alzheimer's by reducing Aβ24 levels.
Yanagawa et al[30]	Correlations between group HbA1C and immediate memory(-ve correlation) FBS and executive function (+ve correlation) GIR and delayed memory (+ve correlation)	Reducing IR and HbA1c levels may be associated with improvements in executive function and memory in T2D;
Anderson-Hanley et al[31]	Cognitive measures: Improved scores in CT (p=0.007) A.G (DM group) ↑ executive function(p=0.02) No improvements in other tests.	Exercises including cyber cycling are beneficial for improving executive function in T2DM.

*= effects did not persist at 12 month

Table 4 Summary of results of experimental studies on effects of exercise cognitive function in T2DM.

correlation was found between fasting blood glucose and set shifting and also between glucose infusion rate and delayed memory. HbA1c levels and immediate memory showed a negative correlation.[30]

Anderson-Hanley et al investigated the effects of cyber cycling and stationery cycling on cognitive function among diabetics and non-diabetics. The participants followed exercise training for 45mins per session for 5days/week for 3 months. The tools used to measure executive functions included color trail, Stroop c test and digit span backwards. (table 3) Results as shown in table 4 revealed improvements in color trail test among the DM participants while no significant changes were observed among non-DM participants. Other tests showed no significant improvements in both groups.[31]

SUMMARY

This review found that there is a scarcity of literature concerning the benefits of physical activity for diabetes associated cognitive decline. Cognitive impairments secondary to diabetes mellitus are common and they predispose the elderly to dementia. Exercise and physical activity have shown promising improvements in cognitive function. Regarding diabetics these improvements are also associated with the action of insulin and glycemic control. The occurrence of cognitive decline among patients with T2DM is very likely contributing to the development of diabetes associated risk factors such as insulin resistance and hyperglycemia. The limited body of evidence suggests that structured exercise programs especially aerobics might result in improvements in certain domains of cognitive function including executive function and memory among diabetics. The improvements in cardiorespiratory fitness, BMI and metabolic parameters like insulin resistance, HBA1c are also marked. Furthermore, exercise also has rejuvenating effects on the frontal lobe possibly by decreasing levels of factors like $A\beta_{42}$ that contribute to the pathology of dementia and Alzheimer's disease. So it can be concluded that participating in structured exercise programs for at least 6 months can results in improvements in certain cognitive domains among T2DM patients. There is a need for future researches that involve studies with larger sample sizes, longer durations and parameters to evaluate the exact association between exercise and improvements in cognitive function.

ABBREVIATIONS

RCT= randomized control trial, QES=quasi-experimental study, MMSE= Minimental state examination / SR= story recall test /BVR= Benton visual retention test / TMT=trail making test ST= Stroop color interface test / TS= task switching / V. F= verbal fluency test / SOPT = self-ordered pointing test / CT= color trails test / DSBT= digit span backwards test. WLIM: Word List (immediate memory) / WLDM: Word List (delayed memory) /9 IR=insulin resistance, GIR=Glucose infusion rate. C= course, D= duration, F=frequency, I= intensity, T= treatment.

REFERENCES

1. Standards of Medical Care in Diabetes—2015 Abridged for Primary Care Providers. Clinical Diabetes. 2015;33(2):97-111.

2. Alberti KGMM, Zimmet Pf. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998;15(7):539-53.

3. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a Modifiable Risk Factor for Type 2 Diabetes in Middle-Aged Men. Diabetes Care. 2001;24(9):1590-5.

4. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. Journal of Epidemiology and Community Health. 2000;54(8):596-602.

5. Colberg SR, Albright AL, Blissmer BJ, Braun B, Chasan-Taber L, Fernhall B, et al. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. Medicine and science in sports and exercise. 2010 2010/12//;42(12):2282-303.

6. Feinkohl I, Price JF, Strachan MWJ, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimer's Research & Therapy. [journal article]. 2015 June 10;7(1):46.

7. Ritchie K, Carrière I, Ritchie CW, Berr C, Artero S, Ancelin M-L. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. BMJ. 2010;341.

8. Kawamura T, Umemura T, Hotta N. Cognitive impairment in diabetic patients: Can diabetic control prevent cognitive decline? Journal of Diabetes Investigation. 2012;3(5):413-23.

9. Kodl CT, Seaquist ER. Cognitive Dysfunction and Diabetes Mellitus. Endocrine Reviews. 2008;29(4):494-511.

10. S. Roriz-Filho J, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves MLF, et al. (Pre)diabetes, brain aging, and cognition. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2009;1792(5):432-43.

11. Roberts RO, Geda YE, Knopman DS, et al. Association of duration and severity of diabetes mellitus with mild cognitive impairment. Archives of Neurology. 2008;65(8):1066-73.

12. Luchsinger JA. Type 2 diabetes and cognitive impairment: linking mechanisms. J Alzheimers Dis. 2012;30(2):2012-111433.

13. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. Journal of clinical and experimental neuropsychology. 2004;26(8):1044-80.

14. van den Berg E, Reijmer YD, de Bresser J, Kessels RPC, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia. [journal article]. 2010;53(1):58-65.

15. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. Archives of Neurology. 2012;69(9):1170-5.

16. Logroscino G, Kang JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years. BMJ. 2004;328(7439):548.

17. Rizzo MR, Marfella R, Barbieri M, Boccardi V, Vestini F, Lettieri B, et al. Relationships Between Daily Acute Glucose Fluctuations and Cognitive Performance Among Aged Type 2 Diabetic Patients. Diabetes Care. 2010;33(10):2169-74.

18. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, et al. Glucose tolerance status and risk of dementia in the community: The Hisayama Study. Neurology. 2011 September 20, 2011;77(12):1126-34.

19. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301(15):1565-72.

20. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, et al. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes. Post hoc epidemiologic analysis of the ACCORD trial. 2012;35(4):787-93.

21. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2016;18(2):135-41.

22. Umpierre D, Ribeiro PB, Kramer CK, et al. Physical activity advice only or structured exercise training and association with hba1c levels in type 2 diabetes: A systematic review and meta-analysis. JAMA. 2011;305(17):1790-9.

23. Voss MW, Erickson KI, Prakash RS, Chaddock L, Kim JS, Alves H, et al. Neurobiological markers of exercise-related brain plasticity in older adults. Brain, behavior, and immunity. 2013;28:90-9.

24. The Diabetes Prevention Program (DPP). Description of lifestyle intervention. 2002;25(12):2165-71.

25. kour H, Kothivale V, Goudar S. Exercise and neuro-cognitive functions in patients with diabetes mellitus: A Review. Indian Journal of Health Sciences and Biomedical Research (KLEU). [Review Article]. 2015 January 1, 2015;8(1):6-10.

26. Colberg SR, Somma CT, Sechrist SR. Physical Activity Participation May Offset Some of the Negative Impact of Diabetes on Cognitive Function. Journal of the American Medical Directors Association.9(6):434-8.

27. Devore EE, Kang JH, Okereke O, Grodstein F. Physical Activity Levels and Cognition in Women With Type 2 Diabetes. American Journal of Epidemiology. 2009;170(8):1040-7.

28. Watson GS, Reger MA, Baker LD, McNeely MJ, Fujimoto WY, Kahn SE, et al. Effects of Exercise and Nutrition on Memory in Japanese Americans With Impaired Glucose Tolerance. Diabetes Care. 2006;29(1):135-6.

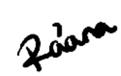
29. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, et al. Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. J Alzheimers Dis. 2010;22(2):569-79.

30. Yanagawa M, Umegaki H, Uno T, Oyun K, Kawano N, Maeno H, et al. Association between improvements in insulin resistance and changes in cognitive function in elderly diabetic patients with normal cognitive function. Geriatr Gerontol Int. 2011;11(3):341-7.

31. Anderson-Hanley C, Arciero PJ, Westen SC, Nimon J, Zimmerman E. Neuropsychological Benefits of Stationary Bike Exercise and a Cybercycle Exergame for

Older Adults with Diabetes: An Exploratory Analysis. Journal of Diabetes Science and Technology. 2012;6(4):849-57.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Raana Ali Mirza	Conceived, designed and did writing of the manuscript.	
2	Irum Yaqoob	Database search, literature review and final editing of the manuscript