The Effect of Aerobic Exercise on Cognitive Function in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

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ABSTRACT

Background • Diabetes, a chronic disease metabolic disorder, commonly affects people. It is well-documented that aerobic exercise significantly reduces blood glucose in diabetic conditions. This study aimed to demonstrate the role of aerobic exercise on T2DM patients and cognitive impairment.

Methods • We selected studies that published random controlled trials (RCTs) on the effects of aerobic exercise on cognitive function in patients with T2DM. However, the animal trials were we excluded in this study. We retrieved the data of random controlled trials from 8 databases based on the influences of aerobic exercise on cognitive function in patients with type 2 diabetes mellitus (T2DM). We utilized RevMan 5.3 software to analyze the data after evaluating the literature.

Results • We selected 685 studies based on the information in the abstract and title after deleting the duplicate references. Then, we investigated the full text of 15. After full-text evaluation,we selected 10 random controlled trials to perform this comprehensive meta-analysis. We found that 10 studies derived the information of cognitive function between the test and the control groups and the cognitive function is significantly higher in the experimental group (SMD: 1.88; 95% Cl: 0.91,2.84; $P < .01$) than the control group. Moreover, the experimental group showed significantly higher minimum mental state examination (MMSE) (SMD: 2.06; 95% Cl: 0.96,3.14; $P < .01$) and Montreal Cognitive Assessment (MoCA) (SMD:1.62; 95% Cl: 0.54, 2.69; $P < .01$) than the normal group.

Conclusion • Our findings demonstrated that aerobic exercise is crucially potent in T2DM patients and cognitive impairment, as evidenced by total cognitive function, MMSE, and MoCA. The above results should be warranted to verify with sophisticated clinical trials. In the future, aerobic exercise is suggested to guide patients'srecovery. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Diabetes is a common chronic disease of metabolic disorders. The incidence of diabetes mellitus is increasing year by year and is becoming more prevalent with rapid global economic development, changing lifestyles, and aging problems. Diabetes is now the most prevalent disease in the world. Recently, the widespread health concern for the mass population is diabetes worldwide. It has become the 6th most deadly disease in the world disease in the world.[1] The development of complications ultimately leads to death. The majority of deaths are allocated to cardiovascular disease (approximately 70%), with ischaemic heart disease accounting for 50% of these deaths. The cost of type 2 diabetes in 2007 was $172 billion in the USA without including the cost of complications.[2] This does not include the indirect costs of complications. Among the world's population, diabetes accounts for more than 9% of them. China has a huge diabetes population, with type 2 diabetes accounting for more than 90% of the total number of adults with the disease. This is why interventions such as exercise, diet, and medication for people with T2DM, especially the middle-aged and aged, are urgently needed.[3]

Diabetes mellitus is comprised of a set of clinical syndromes featured by hyperglycemia, which is inferred by various factors, including genetic factors and environmental factors. The major type of diabetes is type 2 diabetes, which is characterized by insulin deficiency and insulin resistance. It was revealed that diabetes is a crucial complicated factor for impairing cognitive dysfunctions such as mild cognitive impairment (MCI) and dementia, which can significantly increase the complications of cognitive impairment,[4] and cognitive impairment in patients with diabetes is Cognitive impairment is often overlooked in the management of diabetes.[5] Mild cognitive impairment (MCI) is an intermediate condition between normal aging and dementia and is a type of cognitive impairment syndrome. The diabetic and hypoglycemic patients will be increased to 642 million and 481 million by 2040, respectively, and the prevalence of diabetes and hypoglycemia will reach 10.4% and 7.8%.[6] In the same year, the number of dementia patients will be increased to 46.8 million worldwide, of which 9.5 million will be increased in China. It is expected that dementia patients will nearly double every 20 years, rising to 131.5 million by 2050. The development of diabetes with dementia affects social development, as diabetes accelerates the progression of MCI to dementia.[7] The development of diabetes and dementia will have a significant impact on social development.

It was revealed that the expansion of cognitive impairment in type 2 diabetes is associated with a variety of factors: age, education, gender, exercise, interaction with others, tea consumption, sleep disturbances and glycemic variability.[8] Also, glycated hemoglobin levels, duration of diabetes, serum Ghrelin, Visfatin, Insulin Resistance Index (HOMA-IR), Brain-Derived Neurotrophic Factor (BDNF), and the presence of retinopathy with diabetes were also related to type 2 diabetes. The following are major causes of diabetes mellitus (DM): the duration of diabetes mellitus, serum Ghrelin, Visfatin, Insulin Resistance Index (HOMA-IR), Brain-Derived Neurotrophic Factor (BDNF), diabetic retinopathy, diabetic nephropathy, combined hypertension, stroke, family history of DM and hypertension, previous history of dementia in a family member and APOEε4 genotype.[9-11] Sabayan[12] suggests that lifestyle improvements can be made by increasing exercise, eating a healthy diet, getting enough sleep, and quitting smoking. The Lancet report 2017 Dementia Prevention Resolution Report[13] published states that active children's education, exercise, maintaining social engagement, reducing smoking, hearing loss, depression, and managing risk factors such as diabetes and obesity may delay or prevent one-third of people with dementia.

Decreased memory capacity is a major feature of cognitive impairment in diabetic patients[14] and can be accompanied by impairment in various cognitive domains, such as executive, visuospatial, naming, attentional, and abstraction skills. The usual screening scale for cognitive impairment is the Mini-mental State Examination (MMSE), developed by Folstein in 1975, and covers orientation, memory, attention, numeracy, language, and visuospatial capabilities. However, it is of limited use in identifying normal elderly people with MCI and MCI with dementia. The Montreal Cognitive Assessment (MoCA) was developed by Professor Nasreddin in 2004, based on the Reference and Brief Mental State Inventory, to screen for mild cognitive impairment quickly. It covers eight cognitive domains. The 2018 edition of the Dementia and Cognitive Disorders Guidelines[15] again recommends that the Brief Mental State Inventory can be used in conjunction with other tests or the Montreal Cognitive Assessment Scale to augment the diagnostic capacity of MCI.

At present, various pieces of research on exercise for diabetics, mainly on how intense, how long, what kind of exercise, and how often it is appropriate. It is well-documented that aerobic exercise significantly reduces blood glucose in diabetic conditions. Furthermore, the middle-aged and elderly are a special group with poorer physical function and weaker resistance and are unable to perform heavy exercise training, which needs to be done slowly and in conjunction with dietary and pharmacological interventions to delay and improve the progression of diabetes. However, how to maintain the effects of exercise is still a focus that needs further study.

This study aimed to demonstrate the role of aerobic exercise on T2DM patients and cognitive impairment.

MATERIALS AND METHODS

Selection of Studies

We selected studies that published random controlled trials (RCTs) on the effects of aerobic exercise on cognitive function in patients with T2DM. We collected the information from the beginning of the library until July 2022. However, we excluded the animal trials in this study.

Participants of this study

Cognitive impairment in patients with T2DM; Patients aged 18-60 years; Symptoms include Polydipsia, frequent urination, and unexplained weight loss.

Types of Interventions

The intervention group received aerobic exercise or aerobic exercise combined with other therapy to treat T2DM patients and cognitive impairment, and the normal/control group received control or control combined with other therapy.

Types of Outcome Measures

Our outcome indicators are T2DM patients with cognitive impairment. Based on research, the assessment tools for aerobic exercise on cognitive function in patients T2DM patients are (1) Mini-Mental State Examination (MMSE) and (2) Montreal Cognitive Assessment (MoCA).[15] MMSE is a simple mental State Examination scale, the full English name is Mini-mental State examination. It is a commonly used neuropsychological examination tool in clinical practice, which is of great significance for the diagnosis and differential diagnosis of cognitive function decline and dementia, and can reflect the mental state and cognitive function decline of the test subjects more comprehensively and quickly. The Montreal Cognitive Assessment Scale (MoCA) was developed by Professor Nasreddine in 2004. An assessment tool for rapid screening for Mild Cognitive Impairment (MCI) in the areas of attention and concentration, executive function, memory, language, visual-structural skills, abstract thinking, and computation and orientation on a scale of 30 points. The test results showed that the normal value was ≥26 points. We evaluated outcome measures of selected literature using at least one of the above scales.

Search Strategy

The computer retrieves information from the databases, including Cochrane Library, PubMed, EMbase, Web of Science, CNKI, China Biomedical Literature Database (CBM), VIP, and WanFang. The search term is "type 2 diabetes mellitus", "cognitive function," and "exercise". We collected the information from the beginning of the library until July 2022. We followed the following criteria for searching literature: (1) we searched the associated studies by using Chinese and English databases by reading the title of the study, abstract of the study, and Keywords; (2) We used "MeSH Terms" in English databases for identifying the subject terms, the combination of subject words, and keywords.

Extraction and Assessment of data quality

We screened the literature by reading the abstract and selected the studies by reading the full text after the preliminary screening of the abstract. Two researchers of this study independently finalized the selection procedure. If any dispute happened between the two researchers, our third researcher read the studies until the results were agreed upon. Our extracted information included basic findings of the study, study types, the object of the research, size of the sample, the content of the intervention, measures of outcome, etc.

Computational investigation

We performed the analysis of this study by utilizing Review Manager (RevMan) software. If the scores are different between the groups, we identified the standardized mean difference (standardized mean difference, SMD) and 95% letters to the zone (confidence interval, CI) as an indicator of effect. We utilized Chi-square tests to determine whether there is heterogeneity between studies. If $P > .1$ and $I^2 < 50\%$, our study is considered to be more homogeneous, and we employed a fixed-effects model for this computational analysis. If $P < .1$ and $I^2 \geq 50\%$, our study is considered to be heterogeneous and we analyzed heterogeneous sources. If there is no clinical heterogeneity, we employed a random-effects model to investigate this computational study. Furthermore, we evaluated the possible differences in qualitative factors among the subgroups.

Statistical analysis

Continuous normally distributed data are expressed as the means ± SDs. All statistical data were carried out with SPSS statistical software. For multiple comparisons, data were analyzed via analysis of variance (ANOVA) with the Tukey-Kramer Multiple Comparisons Test. $P < .05$ were considered significant differences.

RESULTS

Results of searching

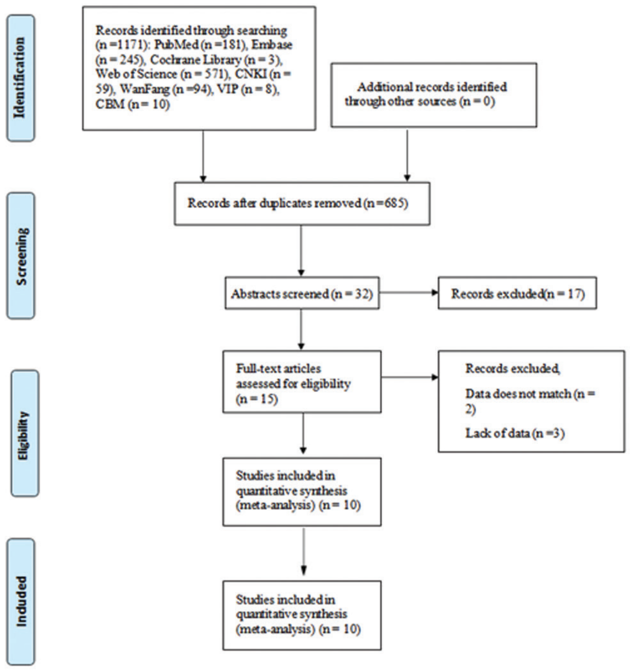
According to the selection criteria, we selected 1171 references. We selected 685 studies based on the information in the abstract and title after deleting the duplicate references. Then, we investigated the full text of 15. We removed 5 records after full-text evaluation for the following causes: mismatch of provided data (n=2) and missing data (n=3). Ultimately, we selected 10 references[16-25] for this meta-analysis (Table 1). We presented the flow chart of the PRISMA statement of this study in Figure 1.

Table 1. The basic characteristics of the included studies.

Study (ref.)	Sample Size (T/C)	Man/ Woman	Age (years)(Mean±SD) (T/C)	T	C	Main Outcomes
Molina, 2021[16]	38/38	0/76	72.6±3.9/72.2±4.3	Aerobic Exercise	Control	MMSE
Matveeva, 2019[17]	30/30	21/39	58.7±11.5/56.0±11.0	Aerobic Exercise	Control	MoCA
Yamamoto, 2020[18]	18/17	19/16	73.2±2.6 / 73.3±2.5	Aerobic Exercise	Control	MMSE
Liang, 2017[19]	50/50	52/48	62±5. 223/65±6. 112	Aerobic Exercise	Control	MMSE
Zhang, 2019[20]	29/21	22/28	70.82±6.03/77.25±6.90	Aerobic Exercise	Control	MMSE, MoCA
Zhang, 2017[21]	36/38	34/40	69.53±8.02/69.79±6.74	Aerobic Exercise	Control	MoCA
Liu, 2020[22]	128/128	138/118	76.8±4.2/77.2±4.0	Aerobic Exercise	Control	MMSE, MoCA
Wang, 2015[23]	43/46	None	None	Aerobic Exercise	Control	MMSE, MoCA
Yan, 2020[24]	40/42	41/41	65.73±3.99/ 68.07±5.47	Aerobic Exercise	Control	MMSE, MoCA
Rao, 2018[25]	100/100	112/88	58.01±3.57/ 57.88±3.76	Aerobic Exercise	Control	MMSE

Abbreviations: T, trial group; C, control group. MMSE:Mini-mental State Examination; MoCA, Montreal Cognitive Assessment.

Figure 1. Flow Chart.



Total cognitive function

All of the 10 studies provided the total cognitive function of the comparing groups. We found the significantly higher cognitive function of the experimental group (SMD: 1.88; 95% Cl: 0.91, 2.84; $P < .01$, Figure 2) when compared with the normal group. We performed the analysis of the Funnel chart for the total cognitive function (Figure 3). Since we found the level of heterogeneity is high, we investigated the sensitivity analysis (Figure 4). In the experimental group, aerobic exercise improves the total cognitive function in patients with T2DM and cognitive impairment.

Figure 2. Forest illustration of total cognitive function.

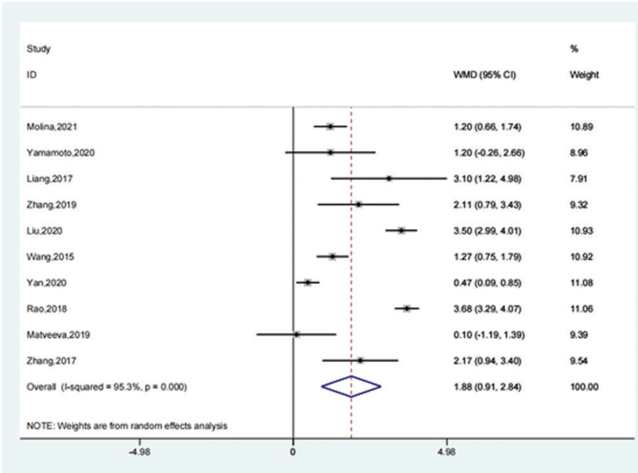


Figure 5. Forest illustration of the duration of MMSE.

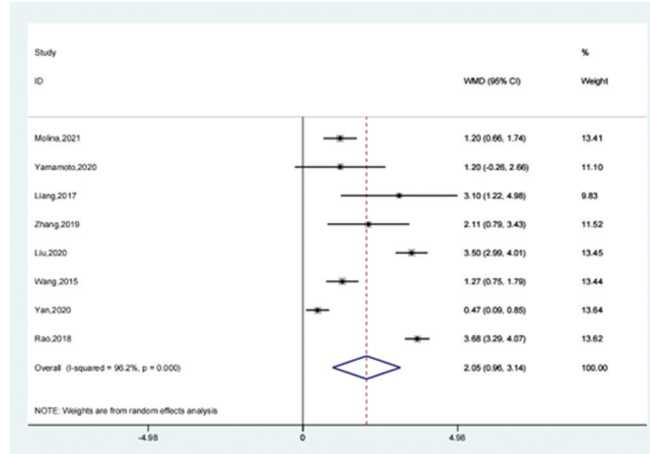


Figure 3. Funnel plot of the length of total cognitive function.

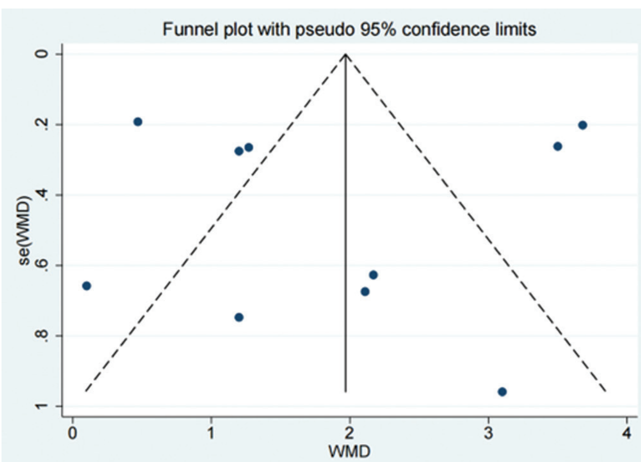


Figure 6. Funnel plot of the duration of MMSE.

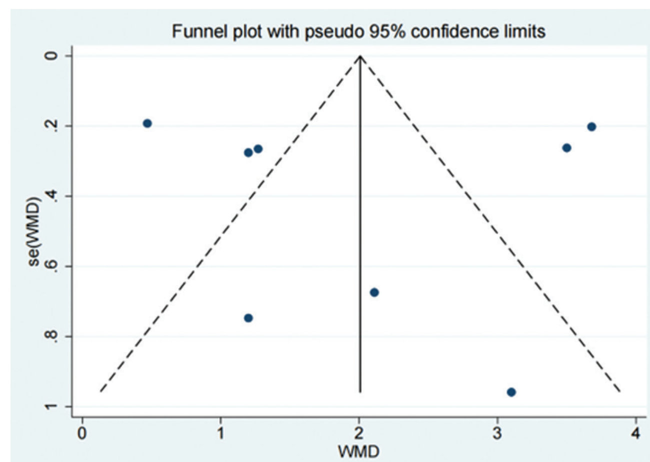


Figure 4. Sensitivity analysis of total cognitive function.

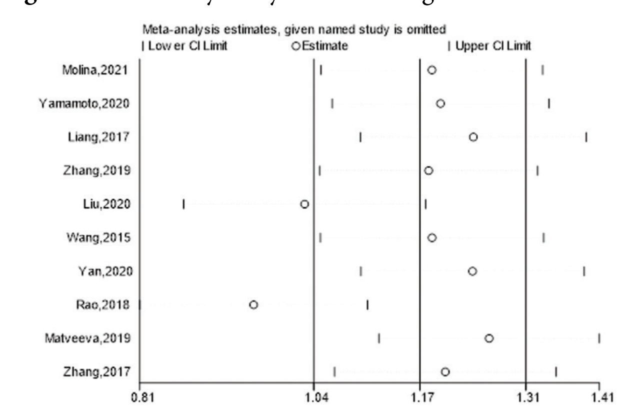
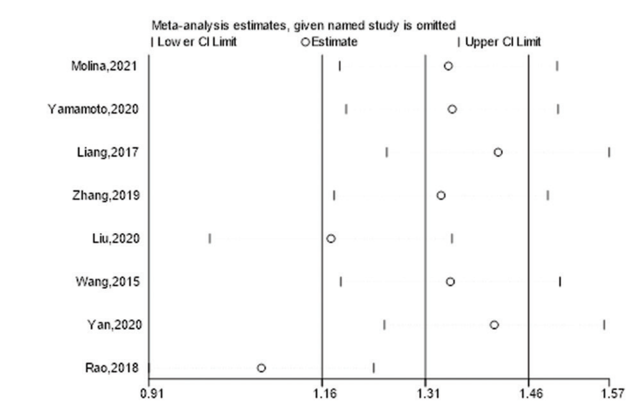


Figure 7. Sensitivity analysis of the duration of MMSE.



Analysis of MMSE

8 studies reported the MMSE information for analyzing and comparing between the groups. We found aerobic exercise significantly improved total cognitive function (SMD: 2.06; 95% Cl: 0.96, 3.14; P < .01, Figure 5) when compared with the normal cases. We investigated the Funnel chart of the MMSE (Figure 6). Since we found the level of heterogeneity is high, we investigated the sensitivity analysis (Figure 7). Aerobic exercise improves the MMSE in patients with T2DM and cognitive impairment in the experimental group. Although the funnel chart shows a relatively asymmetrical distribution of studies, we found that Begg's result is 0.902 and Egger's result is 0.947.

Figure 8. Forest illustration of the duration of c.

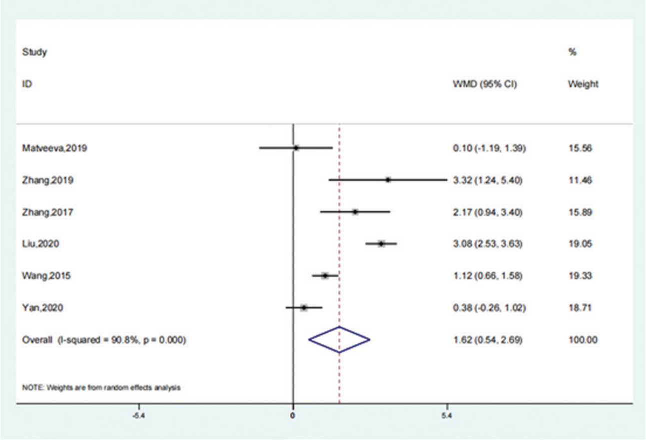
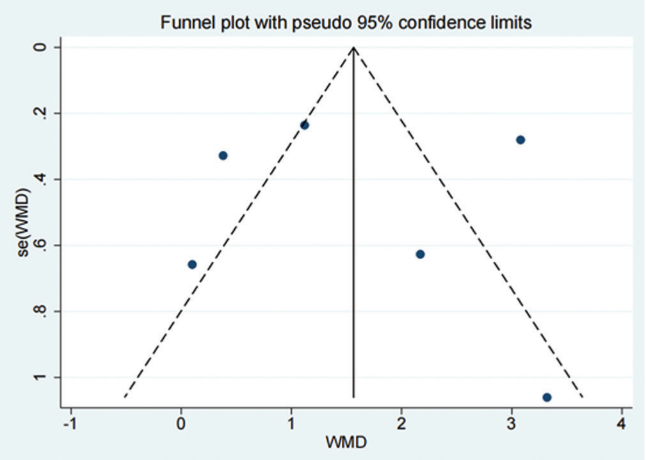


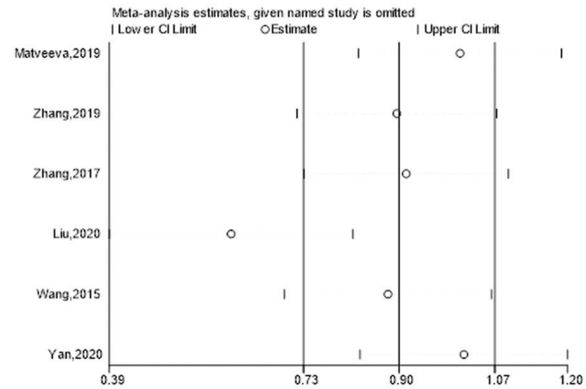
Figure 9. Funnel plot of the duration of MoCA.



Analysis of MoCA

6 references provided the data of MoCA for analyzing and comparing between the groups. The results showed a significantly higher MoCA in the experimental group in comparison with the control group (SMD:1.62; 95% Cl: 0.54,2.69; $P < .01$, Figure 8). There are several commonly used methods for publication bias testing of meta-analysis: funnel plot, Egger test, Begg test (not recommended), etc.We investigated the Funnel chart of the MoCA (Figure 9)and the sensitivity analysis (Figure 10), and found that aerobic exercise improves the MoCA in patients with T2DM and cognitive impairment. Although the funnel chart shows a relatively asymmetrical distribution of studies, we found that Begg's result is 0.304 and Egger's result is 0.942. However, funnel plot asymmetry might suggest publication bias.

Figure 10. Sensitivity analysis of the duration of MoCA.



DISCUSSION

The impact of diabetes on cognitive function

The cognitive function consists of multiple cognitive domains, covering learning, memory, executive, comprehension, and computation. Cognitive impairment is associated with the impairment in single or multiple cognitive domains and is clinically classified as mild, moderate, or severe impairment in cognitive functions and dementia. MCI is related to the impairment in single or multiple cognitive domains and is a fluctuating phase between normal aging and dementia; Vascular cognitive impairment (VCI) refers to a syndrome between MCI and dementia, which is mainly caused by cerebrovascular risk factors, overt or invisible cerebrovascular disease. Unlike MCI, dementia, and VCI, there is no clear definition of cognitive dysfunction in diabetes, but as research progresses, cognitive dysfunction in diabetes is now divided into two categories by classifying the different causes of its onset; one is cognitive dysfunction caused by cerebrovascular disease complicated by diabetes, which is classified as VCI, and the other has no obvious clinical manifestations of cerebrovascular disease, and the mechanisms of cognitive impairment are diverse, similar to Alzheimer's disease (AD). Vascular cognitive impairment (VCI) is a clinical syndrome of stroke or subclinical vascular injury caused by cerebrovascular disease and its risk factors, involving impairment of at least one cognitive domain. Hyperglycemia in diabetes can increase the activity of aldose reductase and activate the sorbitol pathway, causing intracellular hyperosmosis and edema, damaging the structure and function of neuronal cells, and promoting the occurrence of cognitive dysfunction. Various researchers demonstrated that diabetic complications are independent risk factors for impairing cognitive function.[26,27] Nonetheless, cognitive dysfunction in diabetes cannot be considered as a whole. The cognitive dysfunction associated with diabetes varies between types of diabetes.[28] Specifically, type 1 diabetes causes little pathological change in cognitive function compared to its peers[29] and does not lead to substantial cognitive decline over time in the absence of complications.[30,31] It has been reported that 60% to 70% of T2DM cases are diagnosed with impairment in one or more cognitive domains.[32] Based on the fact that T2DM comprises 90% to 95% of all diabetic populations, pathological cognitive dysfunction arising from type 2 diabetes should receive more attention. There are three stages of cognitive impairment depending on the severity of the impairment in T2DM patients: diabetic hypercognition, MCI, and dementia. The term "diabetic cognitive decline" is related to the presence of impairment in single or multiple cognitive domains that is mild enough not to interfere with the patient's capability for managing themselves and living a normal life. Also, changes in cognitive function in T2DM can occur in single or multiple cognitive domains. Moreover, over time, T2DM cases will deteriorate their cognitive function at a rate 50% faster than normal aging.[33]

The role of aerobic exercise

Aerobic exercise is an exercise involving large muscle groups throughout the body with an adequate supply of oxygen and is characterized by lower intensity, longer duration, and no interruptions. There is extensive literature on the intervention of aerobic exercise in the mid to aged population with T2DM, and recently, large-scale population studies demonstrated the usability of aerobic exercise to prevent and treat T2DM.[34] Not only for healthy people but also patients with chronic diseases, it has been documented that exercise of appropriate intensity can lead to a decrease in blood glucose, strengthen the healthy life of patients with T2DM, increase body energy expenditure, improve metabolic process of lipid, diminished the fat level in the body, lead to expansion of lean body mass, boost immunological activities and diminished the occurrence of complexity.[35] Diabetic patients have low insulin sensitivity and higher than normal blood glucose, but aerobic exercise can improve insulin and receptor binding and insulin sensitivity. Xu, et al.[36] demonstrated that long-term small-volume aerobic exercise may lower the peak level of insulin release in diabetic patients and advance the time of peak. The peak of insulin release in diabetic patients can be reduced, and the time of peak occurrence can be advanced. Liu, et al.[37] found that both aerobic and resistance exercises lowered blood glucose levels and improved insulin sensitivity. Liu, et al.[38] found that aerobic and resistance exercise resulted in faster weight and body fat rate loss in diabetic cases.

The efficacy of aerobic exercise for the treatment of diabetes was studied from 2010 to 2014 in two databases, PubMed and China Knowledge Network, and it was found that there were mostly studies on walking, swimming, taijiquan, Baduanjin, and gymnastics. The aerobic exercises chosen by diabetic patients are mainly walking and jogging, which are relatively safe and less likely to cause accidents. In a study of 347 diabetic patients in the USA,[39] walking is related to the reduction of cardiovascular risk, strengthening fitness, blood pressure, and vascular elasticity in diabetic patients, and moderate to prolonged walking also improved body shape, reduced body weight and reduced risk factors in diabetic patients. Among the exercise therapies for diabetes, low-intensity aerobic exercise has been one of the more widely promoted and safer therapies. However, with the advent of strength exercise to treat chronic diseases, it is becoming clear that strength exercise can also be used to treat diabetes.[40-43] The mechanism might be: Exercise can improve the insulin sensitivity of skeletal muscle of diabetic patients, improve the ability of skeletal muscle cells to take up and utilize glucose, improve lipid metabolism, increase the decomposition of lipid mobilization in skeletal muscle, and reduce lipid accumulation in skeletal muscle. Moreover, long-term exercise can induce mitochondrial adaptation of skeletal muscle cells, thereby repairing the damage caused by diabetes to muscle mitochondria.

The findings of our results

Based on the selection criteria, we have selected 10 studies that included 512 cases in the experimental group and 510 normal populations. In the experimental group, we found higher total cognitive function, MMSE, and MoCA after comparing with the controls. We found the significantly higher cognitive function (SMD: 1.88; 95% Cl: 0.91, 2.84; $P <$ .01, Figure 2), MMSE (SMD:2.06; 95% Cl: 0.96,3.14; $P < .01$), and MoCA (SMD:1.62; 95% Cl: 0.54,2.69; $P < .01$) in the experimental group when compared with the normal group.

The novelty of this study was to show that aerobic exercise is crucially potent in T2DM patients and cognitive impairment. In the future, aerobic exercise is suggested to guide patients's recovery. There are some drawbacks to our study: we selected references that are based on only Chinese and English. Therefore, we assumed that incomplete research inclusion and biases were present in our selection procedure of references. The findings in this study warranted more sophisticated validation research through clinical trials before applying it in the practical field.

CONCLUSION

The results demonstrated that aerobic exercise is substantially effective in patients with T2DM and cognitive impairment, as evidenced by total cognitive function, MMSE, and MoCA and our findings warranted the validation through more sophisticated research.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY

The data used to support this study are available from the corresponding author upon request.

REFERENCE

1. Simpson SH, Corabian P, Jacobs P, Johnson JA. The cost of major comorbidity in people with diabetes mellitus. *CMAJ*. 2003;168(13):1661-1667.
2. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care*. 1998;21(7):1138-1145. doi:10.2337/diacare.21.7.1138
3. Lynch J, Helmrich SP, Lakka TA, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med*. 1996;156(12):1307-1314. doi:10.1001/archinte.1996.00440110073010
4. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J*. 2012;42(5):484-491. doi:10.1111/j.1445-5994.2012.02758.x
5. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. *Lancet Neurol*. 2015;14(3):329-340. doi:10.1016/S1474-4422(14)70249-2
6. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*. 2017;128:40-50. doi:10.1016/j.diabres.2017.03.024
7. Hamed SA. Brain injury with diabetes mellitus: evidence, mechanisms and treatment implications. *Expert Rev Clin Pharmacol*. 2017;10(4):409-428. doi:10.1080/17512433.2017.1293521
8. Cui X, Abduljalil A, Manor BD, Peng CK, Novak V. Multi-scale glycemic variability: a link to gray matter atrophy and cognitive decline in type 2 diabetes. *PLoS One*. 2014;9(1):e86284. doi:10.1371/journal.pone.0086284

9. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig*. 2013;4(6):640-650. doi:10.1111/jdi.12087
10. Saedi E, Gheini MR, Faiz F, Arami MA. Diabetes mellitus and cognitive impairments. *World J Diabetes*. 2016;7(17):412-422. doi:10.4239/wjd.v7.i17.412
11. Zhou Y, Fang R, Liu LH, Chen SD, Tang HD. Clinical Characteristics for the Relationship between Type-2 Diabetes Mellitus and Cognitive Impairment: A Cross-Sectional Study. *Aging Dis*. 2015;6(4):236-244. doi:10.14336/AD.2014.1004
12. Sabayan B, Sorond F. Reducing Risk of Dementia in Older Age. *JAMA*. 2017;317(19):2028. doi:10.1001/jama.2017.2247
13. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734. doi:10.1016/S0140-6736(17)31363-6
14. Umegaki H, Kawamura T, Umemura T, Kawano N. Factors associated with cognitive decline in older adults with type 2 diabetes mellitus during a 6-year observation. *Geriatr Gerontol Int*. 2015;15(3):302-310. doi:10.1111/ggi.12273
15. China Dementia and Cognitive Impairment Diagnosis and Treatment Guidelines Writing Group, Cognitive Impairment Disorders Committee, Neurologist Branch, Chinese Medical Association. 2018 Chinese guidelines for the diagnosis and treatment of dementia and cognitive impairment(V):Diagnosis and treatment of mild cognitive impairment [J]. *Chin Med J (Engl)*. 2018;98(17):1294-1301.
16. Molina-Sotomayor E, Gómez-Campos R, Ulloa-Tapia E, et al. Efectos de un programa de entrenamiento de marcha sobre las capacidad aeróbica y la función cognitiva en mujeres diabéticas de edad avanzada. [Effects of physical exercise on aerobic fitness and cognition in older women with type 2 diabetes mellitus]. *Rev Med Chil*. 2021;149(1):37-44. doi:10.4067/S0034-98872021000100037
17. Matveeva MV, Samoilova YG, Zhukova NG, Ratkina KR, Yakimovich IY. Raznye vidy reabilitatsii kognitivnoĭ disfunktsii u patsientov s sakharnym diabetom 2-go tipa. [Different types of cognitive rehabilitation in patients with type 2 diabetes]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2019;119(8):12-17. doi:10.17116/jnevro201911908112
18. Yamamoto Y, Nagai Y, Kawanabe S, et al. Effects of resistance training using elastic bands on muscle strength with or without a leucine supplement for 48 weeks in elderly patients with type 2 diabetes. *Endocr J*. 2021;68(3):291-298. doi:10.1507/endocrj.EJ20-0550
19. Liang CM, An G, Han XT, Ma DH, Sun Y. The effect of metformin combined with aerobic exercise on the improvement of cognitive function in patients with type 2 diabetes mellitus [J]. *Zhongguo Laonianxue Zazhi*. 2017;37(12):2958-2959.
20. Zhang YF. *Effect of metformin combined with aerobic exercise on cognitive function in elderly patients with type 2 diabetes mellitus.* [D] Shanxi Medical University; 2019.
21. Zhang MP, Wang JY, Chen J, She YW, Chen L, Cheng J. Effect of rehabilitation intervention on cognitive function in elderly patients with type 2 diabetes mellitus with mild cognitive impairment [J]. *Chinese Journal of Geriatric Multiorgan Diseases*. 2017;16(01):23-27.
22. Liu L, Yan YJ. Clinical efficacy of aerobic exercise combined with metformin in elderly type 2 diabetes mellitus and the effect on its cognitive function[J]. Chinese primary health care,2020,34(04):87-89.
23. Wang J, Zhang Y, Chen SW, et al. Effects of nourishing gong on cognitive function and inflammatory factors in elderly patients with type 2 diabetes in the community [J]. *Medical Clinical Research*. 2015;(3):439-442.
24. Yan J. *Effects of aerobic exercise on cognitive function and functional brain structure in patients with type 2 diabetes mellitus.* [D] Nanjing University of Traditional Chinese Medicine; 2020.
25. Rao F,Peng CH. Effects of long-term lifestyle intervention on cognitive function in patients with diabetes mellitus[J]. China urban and rural enterprise health,2018,33(10):6-9.
26. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. *Lancet Neurol*. 2015;14(3):329-340. doi:10.1016/S1474-4422(14)70249-2
27. Zhang J, Chen C, Hua S, et al. An updated meta-analysis of cohort studies: diabetes and risk of Alzheimer's disease. *Diabetes Res Clin Pract*. 2017;124:41-47. doi:10.1016/j.diabres.2016.10.024
28. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol*. 2008;7(2):184-190. doi:10.1016/S1474-4422(08)70021-8
29. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care*. 2005;28(3):726-735. doi:10.2337/diacare.28.3.726
30. Ryan CM, van Duinkerken E, Rosano C. Neurocognitive consequences of diabetes. *Am Psychol*. 2016;71(7):563-576. doi:10.1037/a0040455
31. Nunley KA, Rosano C, Ryan CM, et al. Clinically Relevant Cognitive Impairment in Middle-Aged Adults With Childhood-Onset Type 1 Diabetes. *Diabetes Care*. 2015;38(9):1768-1776. doi:10.2337/dc15-0041
32. Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? *Diabetes*. 2014;63(7):2244-2252. doi:10.2337/db14-0348
33. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2018;14(10):591-604. doi:10.1038/s41574-018-0048-7
34. Weinstein AR, Sesso HD, Lee IM, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA*. 2004;292(10):1188-1194. doi:10.1001/jama.292.10.1188
35. Hopkins D. Exercise-induced and other daytime hypoglycemic events in patients with diabetes: prevention and treatment. *Diabetes Res Clin Pract*. 2004;65(suppl 1):S35-S39. doi:10.1016/j.diabres.2004.07.009
36. Xu GQ, Lin W, Du XY, et al. Effect of exercise therapy on blood glucose in patients with type 2 diabetes mellitus[J]. Chinese Journal of Sports Medicine,2002,21(3):284-286,277.
37. Liu ZT. Effect of different exercise modalities on blood glucose related indexes in type 2 diabetic patients [J]. *Journal of Shandong Institute of Sports*. 2010;26(7):46-51.
38. Li S. *Study on the effect of strength aerobic exercise prescription on glucose and lipid metabolism in type 2 diabetic patients.* [D] Beijing University of Sports; 2003.
39. Kurian J, Mohanthy S, Nanjumdaiah RM. Jintu Kurian 1, Soubhagyalaxmi Mohanthy 2, Ramesh Mavathur Nanjumdaiah. Mechanism of action of yoga on prevention and management of type 2 diabetes mellitus: narrative review. *J Bodyw Mov Ther*. 2022;29:134-139. doi:10.1016/j.jbmt.2021.10.003
40. Nery C, Moraes SRA, Novaes KA, Bezerra MA, Silveira PVC, Lemos A. Effectiveness of resistance exercise compared to aerobic exercise without insulin therapy in patients with type 2 diabetes mellitus: a meta-analysis. *Braz J Phys Ther*. 2017;21(6):400-415. doi:10.1016/j.bjpt.2017.06.004
41. Reddy R, Wittenberg A, Castle JR, et al. Effect of Aerobic and Resistance Exercise on Glycemic Control in Adults With Type 1 Diabetes. *Can J Diabetes*. 2019;43(6):406-414.e1. doi:10.1016/j.jcjd.2018.08.193
42. Yang Z, Scott CA, Mao C, Tang J, Farmer AJ. Resistance exercise versus aerobic exercise for type 2 diabetes: a systematic review and meta-analysis. *Sports Med*. 2014;44(4):487-499. doi:10.1007/s40279-013-0128-8
43. Lu X, Zhao C. Exercise and Type 1 Diabetes. *Adv Exp Med Biol*. 2020;1228:107-121. doi:10.1007/978-981-15-1792-1_7