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Effect of structured physical therapy program on patients with diabetes and mild cognitive impairment: randomised controlled trial

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Abstract

Introduction. The mild cognitive impairment (MCI) refers to a condition that falls in between dementia and the normal cognitive ageing process. Aim of the study: to explore how a physical therapy rehabilitation program affected patients with type 2 diabetes mellitus (T2DM) and MCI.

Methods. The study included 37 elderly patients with T2DM and MCI from Al-Azhar University Hospital aged from 60 to 75 years old. After a physician's referral, they were randomly allocated into two groups. Group A: 27 patients, underwent a three-session per week, 60-minute physical therapy rehabilitation program in addition to medical treatment. The twelve-week program also included resistive exercise, stretching exercises, and aerobic treadmill walking. The 10 patients in Group B only received medical treatment for a total of twelve weeks. Researchers assessed Glycosylated haemoglobin (HbA1c), the p300 neurophysiological test, Mini-Mental State Examination (MMSE) scale, and Montreal Cognitive Assessment (MOCA).

Results. There were significantly decreased HbA1c and P300 post-treatment compared to pre-treatment within the study group ($p = 0.0001$ and $p = 0.0001$, respectively) and control group ($p = 0.005$ and $p = 0.0001$, respectively). The MOCA significantly increased post-treatment compared to pre-treatment within the study group, but there was no significant difference in the MOCA between pre- and post-treatment in the control group. The study group had decreased HbA1c, and increased MMS, MOCA, and P300 (13.72, 19.34, 18.7, and 7.2%, respectively) compared to the control group (11.06, 11.06, 9.3, 5.98%, respectively).

Conclusions. Physical therapy rehabilitation programs are important in helping patients with T2DM for improving their memory and cognitive function as well as decreasing the MCI progression.

Key words: diabetes mellitus, cognitive dysfunction, rehabilitation program, mental status and dementia tests

Introduction

Poor cognitive function can be caused by chronic diseases, including diabetes, vascular disease, and its consequences, such as neuropathy [1]. Ischemic and haemorrhagic factors, and other variables impacting functional brain areas, can be implicated in the pathophysiology of vascular cognitive illness. The primary structural change in cerebral vascular disease (CVD)-induced vascular cognitive impairment is grey matter atrophy and disturbances in the white matter of the brain [2]. Also, type 2 diabetes mellitus (T2DM) has the potential to double the incidence of dementia, Alzheimer's disease, and vascular dementia [3]. There are currently 47 million dementia sufferers worldwide, and by 2050, this number is predicted to rise to 131 million [4]. Alzheimer's disease (AD) and T2DM impact a significant proportion of older persons. The International Diabetes Federation estimates that 463 million people globally had diabetes in 2019, with 90% of those cases being T2DM [5]. T2DM and hypertension in middle age have been shown to significantly increase the risk of dementia, even though the associations between dementia and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, triglycerides, obesity, non-alcoholic fatty liver disease (NAFLD), dietary habits, smoking, sedentary lifestyle, and gut microbiota are less clear [6].

In other words, people with mild cognitive impairment (MCI) have a more serious cognitive impairment than would be acceptable considering their age and degree of education a decade later. MCI is a state of cognitive performance that exists between the overall decrease seen in healthy ageing and that shown in dementia [7]. Patients with MCI are considered to be in a high-risk group because they experience dementia at a rate of 10% to 15% annually, as opposed to 1% to 2% in the overall population. Identification of possible MCI protective factors is therefore essential [8]. When compared to people of the same age, someone with MCI exhibits a minor but discernible deterioration in mental capacities (memory and thinking skills). MCI is the term used to describe the early phase of memory problems or other cognitive skill loss in persons who are still able to do the bulk of daily tasks on their own. These individuals may also have spatial/visual perception or language loss. Amnestic MCI, which mainly affects memory, and non-amnestic MCI, which impairs cognitive abilities other than memory, are the two main categories of MCI based on the thinking skills impacted [9].

New therapeutic strategies are required for MCI as pharmacological treatments have minimal to no impact on the disease [10]. In medical practice, cognitive screening tests are useful as a first step in assessing individuals with MCI, followed by formal neuropsychological testing [11]. The inter-

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ventions for MCI have two purposes: symptomatic relief, while enhancing the cognitive abilities and reducing the non-cognitive symptoms; and disease adjustment or delaying the onset of clinically evident dementia by stopping or delaying future cognitive decline [12]. The early detection of MCI can assist medical professionals in managing complications. Patients with diabetes are more likely to acquire Alzheimer's disease (AD), dementia, and other types of degenerative memory loss if the condition is not effectively treated [13]. The existing neuroplasticity still allows for the reversal of neurological degeneration in the MCI stage, which is an intermediate condition between normal cognition (NC) and dementia. Interventions for MCI patients are therefore more important for public health compared to those for dementia patients [14].

The P300 is a large positive event-related potential (ERP) component elicited by changes in the neural representation of a stimulus' context. The amplitude of P300 can be viewed as a measure of central nervous system activity that reflects the processing of incoming information when memory updating is engaged. P300 latency is considered to be an index of the stimulus classification speed, as well as a sensitive temporal measure of neural activity underlying attention allocation and immediate memory. Many studies have shown that P300 latency may also be a sensitive index of the efficiency of many cognitive functions. Moreover, P300 latency gets longer with ageing, in parallel with age-related cognitive declines [15].

This study aimed to assess how a physical therapy rehabilitation program affected patients with T2DM and MCI.

Subjects and methods

A single-blinded, randomised, controlled clinical study was the design and setting. All patients gave their written, explicit agreement for the publication of their personal information and anonymous data. This randomised clinical trial was carried out in line with CONSORT recommendations and contains a completed CONSORT flow chart [16].

Participants

A specialised neurologist recommended physical therapy to 60 chronic diabetes patients who had MCI. Those with scores ranging from 19 to 23 on the Mini Mental Scale, a positive attitude towards medical care and a HbA1c level of 6.5% or higher, which is considered chronic diabetes, were included in the study. Exclusion criteria were patients who had scores of less than 19 on the Mini Mental State Examination cognitive impairments, MCI brought on by medication side effects, infection outside the brain, stroke, brain cancer, or musculoskeletal disorders that restrict the patient's ability to participate in therapeutic exercises, as well as any patient taking any medication that may impair cognition, such as antiepileptic and antipsychotic drugs, which are conditions that may prevent patients from participating in therapy The research was carried out in a clinic for internal medicine between January and August 2022 at Al-Azhar University Hospital.

Randomisation and blinding

The patients were randomly divided into two groups by sealed, opaque envelopes and a computer-generated sequence. As part of the study, 37 diabetic patients with MCI were randomly divided into two groups. Group A: consisted of 27 patients, underwent a three-session, 60-minute physical therapy rehab program in addition to medical treatment. The twelve-week program also included resistive exercise, stretching exercises, and aerobic treadmill walking. Group B: consisted of 10 patients who only received medical treatment for a total of twelve weeks. The participants were blinded.

Assessment

To keep a consistent haemodynamic condition during the training program, a careful, written form containing the following information was taken: name, age, address, medications, and measured vital signs before and after each session.

P300 neurophysiological test

Before and after a physical treatment program, the results from the P300 neurophysiological assessment were recorded. The patients were told to keep their eyes open, refrain from eye movement, and count mentally any deviant (rare) random stimuli that appeared among a collection of similar (common) stimuli. Binaural stimulation was used to study P300 waves in order to keep the patients awake. For greater accuracy, a minimum of two tracings with 30 uncommon stimuli each had to be recorded for each patient. The tracings were then combined, and the resulting wave was acquired. 80 decibel hearing loss (dB HL ER-3A) insert earphones were used to deliver the stimuli. Prior to cortical potential analysis, the patients underwent external auditory meatus examination, pure tone audiometry, and acoustic immittance testing while comfortably situated on an armchair and conscious throughout the process.

The investigation began with cognitive assessments:

Montreal Cognitive Assessment (MoCA): The cognitive evaluation determines the existence, degree, and type of cognitive impairment (for example, language versus memory), and it should take into consideration other elements, including anxiety and lack of sleep as well as linguistic, cultural, and educational aspects. The Montreal Cognitive Assessment (MoCA; ranging from 0 to 30; if score = 24–30, a follow-up assessment for screening is indicated) is a frequently used screening tool. In order to detect cognitive impairment early, such as MCI with procedural dysfunction, the MoCA takes around 10 min to administer [17].

Mini Mental Scale (MMS): used to evaluate the patient's body language, speech to identify impairments, and observe any indication of psychomotor abnormalities, such as the psychomotor retardation that is associated with limited movement and slow question-response times.

HbA1c: Before and after the physical treatment program, a glycated haemoglobin (HbA1c) blood test was performed to detect the average blood sugar (glucose) level over the three months of the study, as elevated HbA1c concentrations are a marker of diabetes-related high blood sugar.

Intervention

Physical therapy program

Each patient in group A (n = 27) was directed to begin a warming-up stage for 5–10 min as a form of active movements for the upper and lower limbs, which was part of a rehabilitation program with three stages and three sets each session. Next began the training stage: 15 min of aerobic exercise on a treadmill with incremental speed increases of 2 mph for the first 5 min, 2.5 mph for the next 5 min, and 3 mph for the final 5 min, at a light intensity (11–12) on the Borg Scale of Perceived Exertion (RPE). The second stage also included

resistance training using weighted dumbbells or weighted sandbags to target different muscle groups in the lower and upper limbs depending on the patient's tolerance and degree of weakness. The third stage included stretching exercises for the calf, hamstring, quadriceps, and upper back muscles immediately following each session of the exercise program. At the end of the session, cool-down activities lasting 5–10 min were performed. The whole exercise program was performed three times per week for 12 weeks. In contrast, only medical treatment was given to group B ($n = 10$).

Treatment procedures

Rehabilitation exercise program: The patients were fully instructed about the study and about the rehabilitation program. The sessions included three stages.

Warm-up stage: First, each patient was instructed to perform the warm-up stage for 5–10 min in the form of marching on the spot and then marching forwards and backwards. This included pumping their arms up and down in rhythm with their steps while keeping the elbows bent and the fists relaxed. Then, heel digs were performed by placing alternate heels to the front, keeping the front foot pointing upwards, and punching out with each heel dig, while maintaining a slight bend in the supporting leg. shoulder rolls, keep marching on the spot. After this, the patient was asked to roll their shoulders forwards 5 times and backwards 5 times, then let their arms hang loose by their sides.

Training stage: Next, the training stage started: 15 min of aerobic exercise by walking on a treadmill with an increasing progression in speed, intensity and duration. The exercise load consisted of walking at a speed of 2 m/min for the first 5 min, 5 m/min for the next 5 min, then 8 m/min for the last 5 min. This was walking at a mild intensity (11–12 on the Borg rating of perceived exertion (RPE) scale) while observing the resulting muscle fatigue and breathing rate, as well as the oxygen saturation range (88–93%) and heart rate by pulse oximeter.

Second: This stage used variable-weight dumbbells or weighted sandbags to strengthen lower limb and upper limb muscle groups alternative ways according to the weakness and tolerance of the individual patients with special considerations regarding joint pain instability due to osteoarthritis (OA) or other causes.

Finally: Stretching exercises were performed at the very end of the exercise program after every session for these muscles:

– Calf muscle (patient stood with their hands against the back of a chair or on a wall, with the feet staggered, one in front of the other. They kept their back leg straight and front knee slightly bent, with both feet flat on the ground, then kept the back knee straight and back foot flat on the ground, bent the front knee to lean towards the chair or wall. The stretch time was 30 s and repeated on the other side.

– Hamstring muscle (patient sat on a soft surface, with one leg straight out in front. Their opposite foot was kept against the inner thigh of their straight leg, and their back straight. The patient was asked to lean forward to reach their toes. The stretching time was 30 s and was repeated on the other side.

– Standing quadriceps muscle (patient stood upright and pulled their right foot to their buttocks, kept their knee pointing downwards and their pelvis tucked under their hips throughout the stretch for 30 s, which was repeated on the other side.

– Upper back muscle (patient sat in a chair with their back straight, core engaged, and ankles knees. They were then asked to twist their body to the right by pushing against the right side of the chair with their left hand. This position was held for 30 s then repeated on the other side.

– Chest stretch (patient stood in an open doorway and placed their forearms vertically on the doorframe. They leaned forwards until they felt a stretch through the chest. They held the stretch for 30 s and repeated it on the other side.

Cooling down stage: The final, 5–10 min cool-down stage was the same as the warm-up stage.

The frequency of the whole exercise program was 3 session per week for 12 weeks.

Sample size

The sample size calculation was performed using G*Power 3.1.9.2 (Universität Kiel, Germany). The sample size was calculated based on 0.05 α error and 80% power of the study to demonstrate a significant improvement observed in the total dysfunction score and HbA1c levels at the end of 6 months of interventional therapy ($p < 0.001$) according to a previous study [18]. Seven cases were added to each group to account for any dropout. Therefore, 37 patients were allocated.

Statistical analysis

Data were checked for homogeneity of variance and the normality assumption test. After removing outliers identified using box and whiskers plots, the Shapiro–Wilk test was carried out to see if the data distribution was normally distributed ($p > 0.05$) or not ($p < 0.05$). Furthermore, according to Levene's test for determining the homogeneity of variance. These results made it possible to undertake both parametric and non-parametric analyses. Analyses using parameters were performed on the normally distributed data.

The statistical analysis was carried out using the SPSS software package for Windows, version 25. The mean and standard deviation were used to demonstrate numerical data for age, HbA1c, MMS, MOCA, and P300. Sex statistics in qualitative forms were given as a number and a percentage. The independent t test for comparing ages was used, while the chi-square test was used to compare the sex. MANOVA, or multivariate analysis of variance, is a statistical technique used to compare the evaluated primary variables of interest across several testing populations and measurement intervals. We utilised a mixed design 2 × 2 MANOVA test, and the first independent variable (between subject variables) was the tested group, which had 2 levels (study group vs. control group). Measuring intervals with two levels (pre- and post-treatment) was the second independent variable (within-subjects factor). The MANOVA test's significant F value was utilised as the starting point for the Bonferroni correction test, which compares the tested variables pairwise within and across groups. At the level of probability ($p < 0.05$), each statistical analysis was significant.

Results

In this study, 60 patients were assessed for eligibility, and 23 patients were excluded (5 patients refused to participate, 3 patients with stroke, 6 patients with contraindication to aerobic exercises, 6 patients with MMS < 19 and 3 patients were taking antipsychotic drugs). The remaining 37 patients were randomly allocated into 2 groups (27 patients in the study group and 10 patients in the control group). All allocated patients were followed-up and analysed statistically (Figure 1).

In the current study, a total of 37 patients from both sexes (18 males and 19 females) were distributed randomly into two

Figure 1. CONSORT flowchart of the studied groups

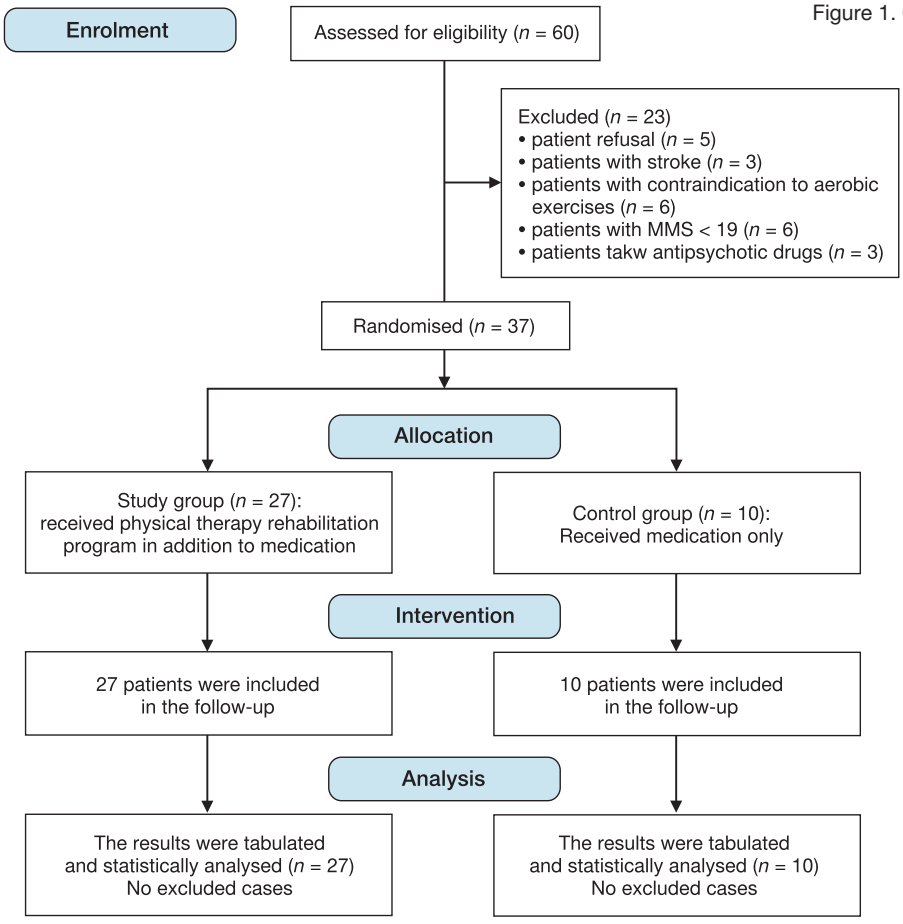

Table 1. Comparison of general characteristics between study group and control group

Items	Study group (*n* = 27)	Control group (*n* = 10)	*p*-value
Age (year)	69.44 ± 3.95	69.70 ± 4.42	0.88
Sex (males : females)	13 (48.10%) : 14 (51.90%)	5 (50.00%) : 5 (50.00%)	0.92

Quantitative data (age) are expressed as mean ± standard deviation and compared by independent *t*-test. Qualitative data (sex) are expressed as number (percentage) and compared by chi-squared test.

Table 2. Comparison of anthropometric data, vital signs, blood glucose and diabetes duration between Study group and Control group

Items	Study group (*n* = 27)	Control group (*n* = 10)	*p*-value
Anthropometric data			
weight (kg)	65.0 ± 5.64	64.0 ± 6.55	0.649
height (m)	1.57 ± 0.05	1.58 ± 0.06	0.795
BMI (kg/m^2)	26.13 ± 2.6	25.69 ± 3.89	0.692
Vital signs			
SBP (mm Hg)	124.81 ± 9.75	128.0 ± 10.33	0.391
DBP (mm Hg)	89.63 ± 9.4	88 ± 7.89	0.629
blood glucose level (mg/dL)	246.7 ± 20.27	234.0 ± 22.94	0.099
diabetes duration (years)	5.7 ± 1.41	6.3 ± 1.25	0.248

BMI – body mass index, SBP – systolic blood pressure
DBP – diastolic blood pressure
Quantitative data (age) are expressed as mean ± standard deviation and compared by independent *t*-test. Qualitative data (sex) are expressed as number (percentage) and compared by chi-squared test.

groups. The results of the patients' demographic data (Table 1) show no significant differences ($p > 0.05$) in age ($p = 0.88$) or sex ($p = 0.92$) between the study group and control group.

As shown in (Table 2), anthropometric measurements (weight, height and BMI), vital signs (SBP and DBP), blood glucose and diabetes duration were insignificantly different between the study group and control group. Also, medications were insignificantly different between the study group and control group.

Statistical multiple pairwise comparison tests (time effect) for HbA1c, MMS, MOCA, and P300 variables within each group (Table 3) showed that HbA1c and P300 significantly ($p < 0.05$) decreased in post-treatment compared to pre-treatment within the study group ($p = 0.0001$ and 0.0001, respectively) and control group ($p = 0.005$ and $p = 0.0001$, respectively).

Time effect had significantly increased MMS post-treatment over pre-treatment in the study group ($p = 0.0001$) and control group ($p = 0.001$). The MOCA significantly ($p < 0.05$) increased post-treatment compared to pre-treatment within the study group ($p = 0.001$), but no significant difference ($p > 0.05$) was observed in MOCA between pre- and post-treatment in the control group ($p = 0.079$). These significant differences in HbA1c, MMS, MOCA, and P300 are favourable for the study group over the control group. Moreover, the study group decreased the HbA1c, and increased the MMS, MOCA,

Table 3. Mixed MANOVA within- and between-groups comparison for HbA1c, MMS, MOCA, and P300

Variables	Items	Study group (n = 27) mean ± *SD*	Control group (n = 10) mean ± *SD*	Change	p-value
HbA1c	Pre-treatment	8.38 ± 0.73	9.22 ± 1.29	0.84	0.06
	Post-treatment	7.23 ± 0.61	8.20 ± 0.73	0.97	0.002*
	Improvement %	13.72%	11.06%		
	p-value	0.0001*	0.005*		
MMS	Pre-treatment	20.11 ± 1.42	19.90 ± 1.19	0.21	0.68
	Post-treatment	24.00 ± 1.46	22.10 ± 1.97	1.90	0.0001*
	Improvement %	19.34%	11.06%		
	p-value	0.0001*	0.001*		
MOCA	Pre-treatment	19.44 ± 1.31	20.4 ± 1.96	0.84	0.095
	Post-treatment	23.07 ± 1.14	22.3 ± 1.49	0.87	0.101
	Improvement %	18.7%	9.3%		
	p-value	0.001*	0.079		
P300	Pre-treatment	319.93 ± 11.23	327.3 ± 15.94	7.67	0.123
	Post-treatment	296.96 ± 9.63	311.50 ± 12.30	14.54	0.001*
	Improvement %	7.2%	5.98%		
	p-value	0.0001*	0.0001*		

* significant ($p < 0.05$)

and P300 (13.72, 19.34, 18.7, and 7.2%, respectively) compared to the control group (11.06, 11.06, 9.3, 5.98%, respectively), which is an improvement.

Statistical multiple pairwise comparison tests (group effect) for the HbA1c, MMS, MOCA, and P300 variables between both groups (Table 3) indicated no significant differences ($p > 0.05$) pre-treatment of HbA1c ($p = 0.06$), MMS ($p = 0.68$), MOCA (0.095) and P300 (0.123) between the study group and control group. However, there were significant differences ($p < 0.05$) post-treatment in HBA1c ($p = 0.002$), MMS ($p = 0.0001$), and P300 ($p = 0.001$), but no significant difference ($p > 0.05$) in MOCA between the study group and control group post-treatment ($p = 0.101$).

Discussion

Numerous studies have demonstrated that physical activity can prevent the onset of degenerative diseases, including Alzheimer's, diabetes, and multiple sclerosis and at least partially repair some of the negative impacts of a sedentary lifestyle [19]. According to the current study, the patients in group A who received medical treatment and an exercise rehabilitation program showed a higher improvement in HbA1c, MMS, MOCA, and P300 than those who received medical treatment only (group B). The current study investigated the effect of a physical therapy rehabilitation program, which consisted of aerobic training on treadmill, resistive exercises, stretching exercise and medical treatment for twelve weeks on the dependent variables. The findings of this research backed those of Liu et al. [20], who proposed that intensive physical exercise therapies for older persons with depressive symptoms could lower their risk of developing MCI.

A recent systematic review and meta-analysis highlighted the significance of including both aerobic and multifaceted activity (such as balance, endurance, strength, or flexibility activities) in the care of individuals with cognitive impairment [21]. In older persons with MCI, six months of aerobic exercise compared to a stretching control enhanced cognitive function [22]. A new meta-analysis verified the benefits of cognitive therapies in delaying cognitive decline in MCI patients, demonstrating the promotion of neuroplasticity and partial stimulation of compensatory scaffolding by memory and multidomain lifestyle modifications [23].

The results of this study are in line with those of Blumenthal et al. [24], who discovered that older adults with cognitive impairment but no diagnosis of dementia saw modest but significant improvements in executive function ($p = 0.32$) and global cognitive functioning ($p = 0.36$) after participating in a physical activity intervention, but no significant improvements were seen in memory ($p = 0.19$) or language ($p = 0.12$). Pedroso et al. [25], who observed that physically active older persons have shorter P300 latency and increased amplitude, confirmed the findings of the current investigation. Exercise, particularly aerobic or resistance exercises, appears to have pronounced positive benefits on P300 in elderly people. Physical activity and exercise, as shown by P300, have been shown to have a favourable impact on cortical activities associated with cognitive abilities in elderly adults.

A recent meta-analysis found that aerobic exercise considerably enhanced overall cognitive function (Mini-Mental State Examination: MD = 0.98, 95% CI [0.5–1.45]; MoCA: MD = 2.7, 95% CI [1.11–4.29]; $p = 0.0009$) and weakly positively enhanced memory (immediate recall: SMD = 0.29, 95% CI [0.13–0.46]; $p = 0.001$). Other cognitive domains showed little to no improvement. According to Zheng et al. [26], aerobic exercise helped persons with MCI enhance their overall cognitive functioning and had a beneficial impact on their memory while having a small effect size. Additionally,

a systematic analysis revealed that aerobic and resistance exercise had no cognitive effects in Alzheimer's disease but had modest favourable effects on executive functioning, attention, and delayed memory in MCI [27].

According to other studies, physical therapy can help MCI patients with their memory and overall cognitive function [28]. Physical therapy has reportedly been shown to slow cognitive deterioration in people with AD or those at risk of it [29]. Nevertheless, two randomised controlled trials found no advantages and reached the conclusion that fitness training did not delay cognitive decline in those with mild-to-moderate dementia. Whereas the exercise training program increased physical fitness, other clinical outcomes did not noticeably improve [30, 31]. Chen et al. [32] examined the effects of Tai Chi Chuan exercise on cognitive function in adults 60 years or older with type 2 diabetes and mild cognitive impairment in China and found that there were no significant differences in other secondary outcomes (DSST, TMT-B, BNT, and ROCF scores, as HbA1c level and HOMA-IR). In the current study, patients with MCI were chosen, which can be reversed with early treatment, but the other studies focused on dementia, which may explain the difference between our results and their findings [33, 34].

Our study had limitations, including a relatively small sample size, for which the psychological status and cooperation of the patients might affect the results of the study, as individual differences between patients affect assessment and treatment outcomes, change in environmental effect on treatment outcomes and we did not use an objective tool for heart rate max, heart rate reserve, or Vo2 reserve, in addition to the RPE.

Conclusions

Physical therapy rehabilitation exercises and medical care have been shown to dramatically improve HbA1c, MMS, and P300 in diabetic patients with MCI. T2DM Individuals with MCI can improve their cognitive function, mental health, and memory.

Availability of data and material

The datasets used and/or analysed during the current study are available as MS Excel files (.xlsx) from the corresponding author upon reasonable request.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by the Ethical Committee and Institutional Review Board (IRB) of the Faculty of Physical Therapy, Cairo University (approval No.: 24/6/2020, P.T.REC/012/002768).

Informed consent

Informed consent has been obtained from all individuals included in this study.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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