Geriatric Nursing 64 (2025) 103434

Contents lists available at ScienceDirect

Geriatric Nursing

journal homepage: www.gnjournal.com

Effect of Baduanjin exercise on lipid profile, blood pressure, and thyroid-stimulating hormone in elderly with subclinical hypothyroidism and mild cognitive impairment: a randomized-controlled trial in women

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ARTICLE INFO

Article history:
Received 1 December 2024
Received in revised form 1 April 2025
Accepted 16 June 2025
Available online xxx

Keywords:
Baduanjin exercise
Lipids
Thyroid-stimulating hormone
Mild cognitive impairment
Subclinical hypothyroidism
Elderly

ABSTRACT

Purpose: Baduanjin exercise's effect on blood pressure, lipid profile, and cognitive function in subclinical hypothyroidism (SCH) women with mild cognitive impairment (MCI) was the aim investigated in forty elderly with mild SCH and MCI.
Methods: Women who administered 12-week levothyroxine medication were randomly assigned to a control group (n=20 SCH women) or Baduanjin-exercise group. Assessment of triglycerides (TG), body mass index (BMI), blood pressure, Addenbrooke's Cognitive Examination III Questionnaire (ACEQ-III), low-density and high-density lipoproteins (LD-lipo, HD-lipo), and cholesterol (CH) was conducted.
Results: All variables improved significantly in both groups. The Baduanjin group's improvements were higher than the control group's improvements. A trend of significant improvements ($P<0.05$) in all variables was achieved toward the group of Baduanjin exercise during the post-value comparison of all variables between SCH groups.
Conclusion: Adding Baduanjin to pharmacotherapies of SCH not only improves blood pressure, TSH, lipids, and BMI, but also improves MCI in older women.

Introduction

It is uncertain if the elevation in thyroid-stimulating hormone (TSH) quantity with age is a physiological adaptive response linked to aging or an actual rise in response to dysfunctional problems. It has also been suggested that the increased frequency of aging-related thyroid abnormalities/dysfunctions is caused by thyroid cells being continually stressed by reactive oxygen species (ROS) required for the synthesis of thyroid hormones, which causes thyroid cellular tissues to undergo oxidative stress (OS), hence mild thyroid failure develops.[1]

Mild thyroid failure, also known as subclinical hypothyroidism (SCH), is a commonly diagnosed thyroid dysfunction in the elderly that affects up to 10% of this population,[2] particularly female older patients.[3] High levels of TSH (> 4.5 mIU/L) with normal levels of free thyroxine hormones (FT4 and FT3) are the defined laboratory diagnosis of SCH.[1]

Subclinical hypothyroidism has detrimental effects on the body's cardio-metabolic processes, which include lowering serum high-density lipoprotein (HD-lipo) and elevating serum cholesterol (CH), triglycerides (TG), low-density lipoproteins (LD-lipo), and blood sugar, causing endothelial dysfunction due to a reduction in the availability of nitric oxide, stiffening of the arterial walls, and raising patients' blood pressure. All of these SCH-induced detrimental changes are important risk factors for hypertension, cardiovascular disease (CVD), and heart failure.[4]

In addition to the newly discovered function/role of thyroxine hormone in controlling/regulating cognitive functions (memory, speech, recalling, reading comprehension, and learning/processing something new) and myelination/growth of the neural system,[5] a growing body of evidence has connected SCH to the pathogenesis of mild cognitive impairment (MCI),[6] the earliest clinical indication/marker of cognitive problems which is accompanied by largely maintained functional activities giving an alarm to start receiving preventative therapy to decrease the chance of developing severe cognitive impairments such as dementia or Alzheimer's diseases.[2] As a result, measuring serum TSH is a highly recommended screening test during the evaluation of the elderly's cognitive deterioration.[6]

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https://doi.org/10.1016/j.gerinurse.2025.103434
0197-4572/$ – see front matter

As a hormone replacement therapy, levothyroxine is the most commonly suggested pharmacological agent of SCH, especially if the levels of TSH exceed 10.0 mIU/L. Levothyroxine not only corrects SCH (via decreasing the levels of TSH) but also improves hypothyroid older patients' lipid profile, adiposity, weight, blood pressure, cognitive skills/mood, memory-related cognitive performance, recalling, speech, reading comprehension, and learning something new.[7]

Recently, literature documented the favorable impact of exercise on the mechanisms of action linked to the deterioration of thyroid dysfunction and its complications in patients with SCH.[8] Besides the reported decrease in the risk of CVD, it has been proved that exercise may correct SCH-related disturbances of lipid profile, TSH,[9] insulin hemostasis/resistance,[10] systolic blood pressure (SBP), and diastolic blood pressure (DBP).11

Baduanjin exercise, a mix of matching body postures, a contemplative mind, and deep breathing techniques in a synergistic fashion or manner, has been practiced in China for more than 1000 years as a traditional mind-body aerobic activity with a low-moderate intensity.[12] In addition to its potential positive effects on osteoarthritis, imbalance, autonomic dysfunctions, hypertension, osteoporosis, and cardiopulmonary dysfunctions in the elderly,[13] Baduanjin exercise approved its capability in regulating blood lipid metabolism to be one of the main recommended therapeutic exercise tools in improving the lipid profile in healthy and cardiovascular-diseased individuals.[14]

Cognitive functions are improved as a result of the added meditative and physical effects of the Baduanjin exercise. In addition to the effect of the physical element on enhancing patients' cognitive functions by stimulating neurophysiological pathways, Baduanjin exercise combines mental and spiritual elements which come into one action during the performance of the physical element, hence Baduanjin exercise is a multi-task exercise that needs a great attentional focus. The simultaneous engagement in a slow and continuous flow of body positions/postures from one movement to the next while considering a proper posture/flexibility of the body, harmonious states of relaxation, and good mental concentration makes Baduanjin exercise an example of a cognitive training procedure because it involves training for visual-spatial processing, attentional focus, and executive functions.[12]

Despite the widespread popularity, the additive benefits of Baduanjin exercise were not utilized in improving lipid profile, blood pressure, cognitive function, and TSH in patients with SCH and MCI. So, this was the first study aimed to investigate the effect of Baduanjin exercise on lipid profile, blood pressure, cognitive function, and TSH in elderly women with SCH and MCI.

Materials and methods

Setting, design, and ethics of this Baduanjin-exercise study

The intervention, the Baduanjin exercise, was supervised in a physiotherapy clinic. This randomized-controlled SCH trial was single-blinded in elderly women with MCI. Helsinki recommendations, consenting elderly with SCH and MCI, and local institutional clearance (the institution of the first author approved the study under a clearance ID: P.T/REC/012/004294) were executed.

Inclusion criteria of SCH women

Mild SCH (TSH $>$ 10 μIU/L) elderly women (n=40) with class-I obesity and MCI were included in this trial. Ages ranged between 65 to 75 years old. With a total score of 100, Addenbrooke's Cognitive Examination III Questionnaire (ACEQ-III) was used to assess the cognitive functions of the participants. Only the participants who scored 83−88 after finishing the scoring of ACEQ-III were included because this score is indicative of the presence of MCI.[15]

Exclusion criteria of SCH women

Elderly SCH women with hepatic disorders, neurological deficits that may affect cognitive functions (stroke, parkinsonism, dementia, *etc.*), respiratory diseases, overt hypothyroidism (TSH $>$ 10 μIU/L, with serum-FT4 concentration below the lower limit of the reference range), heart and kidney disorders were ruled out. Hypertensive and diabetic elderly women were excluded. History of drug dependence (antipsychotics, antidepressants, and sedatives), alcohol drinking, or drug abuse was ruled out.

Randomization of women

The elderly women were randomly recruited from the outpatient clinic of internal disease, Meetghamr General Hospital, to be randomly assigned to 20 women in group A who received Baduanjin exercise (5 times/week, every session was 40 minutes, and every session contained 20 participants who were trained as one group) plus 50-μg daily levothyroxine (administered in the early morning before the women's breakfast) and 20-women group B who received the prescribed dose of levothyroxine only for 12 weeks.

A researcher not involved in prescribing levothyroxine doses or supervising the performance of the Baduanjin exercise assigned the elderly with MCI and SCH to the treatment groups via the enclosed envelope technique. The flow chart of this SCH trial is presented in Fig. 1. The registry number of this SCH trial is NCT05803967.

Baduanjin exercise

This study was conducted during the period from 18 December 2022 to 30 June 2023. A 12-week Badunjin exercise plan with a recurrence of five days per week and a daily duration of 40 minutes was given to group A (the group of Badunjin training and levothyroxine). The "Health Qigong Baduanjin Standard," adopted by the "State Sports General Administration" in 2003, is the source of the training program for the Baduanjin exercise.[16] According to the detailed steps of exercise published in the article of Koh[17] who designed eight sets of actions namely known as the Baduanjin exercise, the following actions were done and supervised in our study as follows: 1) support heaven with your both hands/palms, 2) dragon sprays water with a high force, 3) spread the wings of the big bird, 4) lift window to look at the moon on your left, 5) forcefully descend to earth, 6) the beautiful maiden twists her waist to her right, 7) extend your shoulders to bring your hands together, and finally, 8) dragon claws to your left.

Assessments

Blood pressure, serum TSH (main outcome), HD-lipo, CH, TG, LD-lipo, and body mass index (BMI) were assessed. Also, ACEQ-III was used to assess SCH elderly's cognitive functions. The popular tool, ACEQ-III, is an internationally valid tool that was used to assess MCI. This tool is more accurate than the other popular tools assessing MCI and dementia including Mini-Mental State Examination. Attention (18 points), memory (26 points), language fluency (14 points), visuospatial cognitive ability (16 points), and language (26 points) make up the five areas of cognitive functions assessed by the ACEQ-III. On the ACEQ-III, the perfect typical score is 100 points; a score of 89 represents normal cognitive functions of the assessed participants; a score of 83−88 signifies MCI; and a score of 82 denotes dementia.[15]

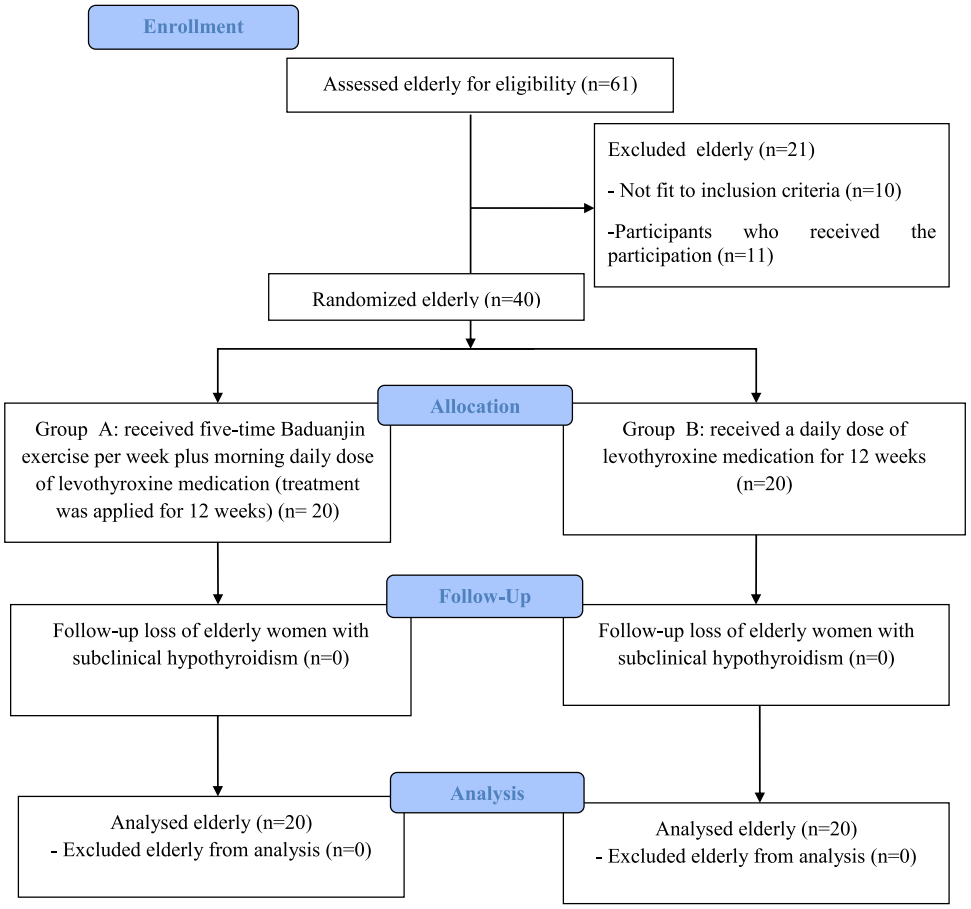

Fig. 1. Flow chart of elderly women with subclinical hypothyroidism.

Blinding

The evaluators of blood lipids, BMI, ACEQ-III, and blood pressure have not informed the nature of SCH interventions (levothyroxine and Baduanjin exercise).

Sample size

To calculate the sample size at power 80%, the authors fixed TSH as a primary outcome of this SCH study in 16 pilot-test elderly women with SCH and MCI. The effect size of TSH (d=1) from G*power analysis detected the need of 17 elderly with SCH and MCI in the group of levothyroxine or the group of Baduanjin exercise plus levothyroxine. Dropout (18%) of the women was avoided by assigning three additional elderly women with SCH and MCI in every group.

Statistical analysis

Regarding the normal distribution of all data of the forty elderly women with SCH and MCI, the Kolmogorov–Smirnov statistic procedure confirmed the normal distribution of data, hence assessing the significant improvements in BMI, TSH, lipid profile, ACEQ-III, and blood pressure within and between groups of SCH and MCI was statistically tested via paired and unpaired tests, respectively, at p-value < 0.05.

Results

Age and BMI (basic data reported in Table 1 did not show significant differences between pre-treatment groups). Also, lipid profile, TSH, ACEQ-III, and blood pressure (clinical pre-treatment outcomes as shown in Table 2) did not show a pretreatment-significant difference between groups was before starting levothyroxine or Baduanjin exercise plus levothyroxine (Table 2) (this was confirmed by the unpaired test).

After analyzing the variables within the levothyroxine group (group B) and Baduanjin-plus-levothyroxine group (group A), all variables (CH, LD-lipo, TG, HD-lipo, BMI, TSH, ACEQ-III, and blood pressure) improved significantly in both groups. The improvements were lower in the levothyroxine group (group B) than in the Baduanjin-plus-levothyroxine group (group A) (Table 2).

When the statistician compared the post values of variables between the levothyroxine group (group B) and the Baduanjin-plus-levothyroxine group (group A), a trend of significant improvements in all variables were reported toward the group of Baduanjin-plus-levothyroxine group (group A) (Table 2).

Table 1
The basic data of postmenopausal class-I obese groups with subclinical hypothyroidism (data are expressed as mean±standard deviation).

Data	Group of Baduanjin exercise plus levothyroxine	Group of levothyroxine	P value*
age [year]	54.60±3.28	53.35±3.19	0.229
Body mass index [kg/m^2]	32.35±1.46	33.21±1.50	0.074

* This is a non-significant P-value (P> 0.05).

Table 2
Outcomes of SCH groups (all data of table 2 are expressed as mean± SD).

Parameters		Group A (Baduanjin exercise plus levothyroxine)	Group B (levothyroxine group)	P-value (between group A and B)
Body mass index (Kg/m^2)	Pre	32.35±1.46	33.21±1.50	0.074
	Post	31.31±1.51	32.85±1.73	0.0048*
	P-value (within SCH groups)	< 0.001*	0.005*	
Total-cholesterol (in plasma, mg/dl)	Pre	227.40±31.41	235.55±34.37	0.438
	Post	189.35±26.36	217.75±36.99	0.008*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Triglycerides (in plasma, mg/dl)	Pre	120.35±18.89	130.35±21.04	0.122
	Post	110.60±14.36	129.05±21.10	0.0025*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Diastolic blood pressure (mmHg)	Pre	82.55±4.22	84.50±3.05	0.102
	Post	76.10±3.14	80.95±4.05	0.0001*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Score of Addenbrooke's Cognitive Examination III	Pre	85.20±1.73	85.60±2.01	0.504
	Post	90.90±4.36	86.95±2.21	0.0009*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Systolic blood pressure (mmHg)	Pre	130.10±7.00	133.20±6.95	0.168
	Post	120.90±6.91	126.15±7.32	0.0001*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Low-density lipoprotein (in plasma, mg/dl)	Pre	147.85±29.17	156.65±25.62	0.317
	Post	122.80±30.60	142.30±23.58	0.029*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
Thyroid-stimulating hormone (μIU/mL)	Pre	12.27±2.34	14.09±3.30	0.051
	Post	5.70±2.54	9.05±3.28	0.0009*
	P-value (within SCH groups)	< 0.001*	< 0.001*	
High-density lipoprotein (in plasma, mg/dl)	Pre	47.50±8.70	41.85±9.17	0.052
	Post	51.20±8.90	45.00±9.27	0.037*
	P-value (within SCH groups)	< 0.001*	< 0.001*	

* When this symbol marks any P value in this table, it means that this P-value is < 0.05 so it is significant. SCH: Subclinical hypothyroidism

Discussion

As a hormone replacement therapy, levothyroxine is the most commonly suggested pharmacological agent of SCH. Levothyroxine not only corrects SCH (via decreasing the levels of TSH) but also improves hypothyroid older patients' lipid profile, adiposity, weight, blood pressure, cognitive skills/mood, memory-related cognitive performance, recalling, speech, reading comprehension, and learning something new. There is usual need for treatment that can be used safely and without side effects. This treatment may be found in physical exercise, including Baduanjin exercises.

Exercise and TSH

This was the first study that utilized the Baduanjin intervention, the low-to-medium intensity aerobic exercise, as an exercise protocol in elderly women suffering from SCH.

Exercise-induced changes in thyroid function tests are complicated physiological reactions that are challenging to fully quantify or explained.[18] Evidence-based literature shows a significant connection between adiposity and TSH level[19] in subclinically hypothyroid patients.[11] There are fewer TSH receptors in obese people, noting that reduction in TSH receptors lowers thyroid hormone levels and raises serum TSH concentration. The hypothalamic-pituitary-thyroid axis is influenced by an exercise-induced decrease of adiposity, which raises thyroid hormone levels. As a result, elevated concentrations of thyroid hormones have a negative feedback action on the pituitary gland and suppress TSH output.[19]

Supporting the documented exercise-induced increase in blood supply to different body parts including endocrine glands, and possibly by increasing thyroid gland perfusion, exercise can enhance thyroid functions (including TSH), however, this requires more research.[20]

Another mechanism connecting TSH secretion to the activity of dopamine receptors in the brain may explain the decrease of TSH in response to exercise-induced weight loss. The release of TSH is connected to the upregulation and activation of dopamine receptors. Both upregulation and activity of these receptors are relatively inhibited in obese patients, so the release of TSH increases. With exercise-induced weight loss, the inhibited upregulation and activity of dopamine receptors are alleviated, and hence the production of TSH becomes low.[19]

Another opinion reports a strong link exists between serum TSH levels and leptin levels[21] due to the interconnection between the hypothalamic-pituitary-thyroid axis and serum leptin.[22] Consequently, a decrease in serum TSH levels following exercise may be a response to exercise-induced control of serum leptin and the hypothalamic-pituitary-thyroid axis.[23]

Referring to another alternative mechanism, exercise boosts metabolic activity in patients with hypothyroidism, which promotes calorie burning from the increased adipose mass. This increase in caloric burning aids in weight loss.[20] Supporting this theory and our results, a previous study reported that the significant 12-week exercise-induced reduction in BMI was associated with a significant decrease in TSH of overweight/obese SCH women.[10] Also, supporting us, the significant reduction of TSH was parallel to the significant loss of body mass after a 30-day exercise protocol (40-60 minutes of daily physical activity along with 40-50 minutes of supervised treadmill walking once weekly) in TSH levels in 50 individuals with SCH.[24] On the other hand, despite the significant decrease in BMI and fat mass, 36-month regular physical activity and whey protein supplementation did not support the role of weight loss in improving TSH because its levels were not improved in overweight/obese middle-aged individuals due to the exclusion of individuals of thyroid dysfunctions.[25]

Also, details of exercise prescription (length and intensity of exercise) and participants' age are mitigating factors in explaining TSH

response to exercise[18] which sometimes come into agreement and disagreement with our presented results.

Regarding the intensity of exercise and age of participants, there was a great unexplained variation of TSH response to exercise. Exercise-induced TSH decrease is best accomplished with medium-intensity aerobic exercise (70% of a person's maximal heart rate like the intensity of the executed Baduanjin exercise in this study) and in middle-aged participants. Regular exercise at this intensity level not only increases weight drop but also contributes to some improvement in thyroid functions.[20] In the study of Bansal et al.[20] which was conducted on 20 hypothyroid men (aged 30-40 years old), serum TSH readings were shown to be considerably lower in patients of the exercise group (n=10, who received 3 months of daily 1-hour medium intensity exercise) ($P<0.001$) than in patients of the non-exercise group (n=10) (P=0.43). On the other hand, after finishing 8 weeks of the concurrent aerobic-resistance program at 80% of hypothyroid girls' maximal heart rate aged 12-17 years old, besides the opposing non-significant improvement of CH, LD-lipo, TG, and HD-lipo, TSH did not show significant changes.[19]

Regarding the length of the prescribed exercise protocol, there was a great unexplained variation in TSH response to exercise. A significant reduction in TSH was recorded after a 5-minute acute exercise (ramp exercise test) in SCH patients (n=53).[23] On the opposite side, Ciloglu et al.[26] documented an increase in the TSH of athletes after performing 9-minute bicycling.

The results of relatively long training (12-week aerobic training) in overweight/obese SCH women were consistent with our results, especially with a significant decrease in LD-lipo, CH, BMI, and TSH due to the improvement in inflammatory markers (C reactive protein) [10]. On the opposite side, studies reported that the different long-term periods of aerobic training (three[11] or six months[27]) did not show a significant decrease in TSH levels of SCH women

Baduanjin exercise, lipids, and blood pressure

Modern basic research documented the ability of Baduanjin exercise in enhancing the ability of lipoprotein lipase to hydrolyze TG, promoting HD-lipo synthesis by boosting the molecular weight of LD-lipo receptor (LD-lipo-R) and increasing LD-lipo-R gene transcription and protein expression on the liver. Through its ability to improve insulin sensitivity and increase the ratio of the energy supply from lipid oxidation, the low-intensity, prolonged practice of Baduanjin exercise could encourage the consumption and metabolism of blood lipids.[14]

Regarding Baduanjin-induced reduction of SBP and DBP, considering this exercise is a fat burner and a weight-loss intervention (recorded by significant improvements in lipid profile and BMI due to energy expenditure consumed by the physical components of prolonged Baduanjin training), the combined loss of fat mass and weight during this exercise can control and/or decrease high levels of blood pressure.[28] Another thought connects the Baduanjin-induced drop in blood pressure to the nature of the relaxing procedure/practice of the exercise that incorporates meditation with mild movements. According to a growing body of research, contents of Baduanjin exercise (meditation, relaxation, and mild movements) alter/modulate the pressure receptors in the aortic arch and/or carotid sinus and contributes to blood pressure reduction and coronary arterial walls' expansion.[29]

Supporting the positive effects of Baduanjin exercise on lipids in our study, a study published in 2020 reported that 12-week Baduanjin training using this exercise significantly reduced BMI and LD-lipo and increased HD-lipo of perimenopausal women.[30] Also, the 1-year Baduanjin exercise significantly improved blood pressure, LD-lipo, TG, TG, weight, and HD-lipo in prediabetics, hence it is another support to our results.[31] Again, adding a 3-month Baduanjin exercise to traditional Chinese nursing interventions magnified TG and CH improvements in the diabetic elderly.[32]

The results of a Baduanjin-exercise systematic review enrolled eight randomized controlled trials documented a significant role of this exercise in improving BMI, LD-lipo, CH, TG, HD-lipo, SBP, and DBP in hypertensive patients.[28] Also, the results of a Baduanjin-exercise systematic review enrolled twelve clinical trials documented the significant role of this exercise in improving SBP and DBP in hypertensive patients.[29] Opposite to our results, 16-week Baduanjin exercise did not improve blood lipid indices (TC, TG, LD-lipo, blood pressure, HD-lipo, and BMI) in healthy subjects.[33]

Baduanjin exercise and cognitive function

An example of aerobic exercise is the Baduanjin (low-medium intensity aerobic exercise). A growing body of research indicates that aerobic exercise benefits MCI patients' cognitive function. Improvement in cognitive abilities is brought on by aerobic exercise because it repeatedly stimulates noradrenergic activity in the brain.[34]

Several imaging studies documented the significant effect of exercise on increasing the volume of cognition-related brain regions (hippocampus, frontal, temporal, and cingulate cortex) and neuroprotective cascades (such as an increase in the concentration of serum brain-derived neurotrophic factor) that are susceptible to age- and disease-related.[35] Also, the mechanism of exercise-induced improvement in cognitive performance/function may be also attributable to the fact that the Baduanjin program's mental process emphasizes self-regulation (or the ability to control one's thoughts/emotions) and that the executive function shares brain circuits/network with self-regulation.[36]

The mind-body workout known as Baduanjin is distinct from more traditional aerobic physical activities like walking or cycling. Completing its multitasking components (posture, breathing, mindfulness, and meditation) needs more concentration and control from the older participants. Training for visual-spatial processing, attentional focus, and executive functions is involved in changing from one posture to another while maintaining harmony with breathing, relaxation, mindfulness, and meditation. As a result, cognitive performance/function rises in older patients with MCI.[34]

Supporting us, the whole-brain functional MRI documented the positive role of the 24-week Baduanjin exercise in improving the MCI elderly's attention.[34] Also, a 12-week Baduanjin training course of 60 minutes per day, five days per week, was discovered to be beneficial in slowing age-related memory loss in healthy older community members.[37] In older adults with or without cognitive impairment, Baduanjin exercise is very helpful in conserving and/or enhancing both global and particular (memory processing speed, executive function, attention, or linguistic learning and memory) areas of cognitive functions.[38] The Functional Assessment of Cancer Therapy-Cognitive Function Questionnaire (FACT-Cog) was the subjective tool used in a recent study to assess cognitive function in response to a 12-week Baduanjin exercise in a recent study published in 2022. The participants, women with breast cancer receiving chemotherapy, showed a significant improvement in FACT-Cog to be consistent with our results.[39]

Physical activity/exercise[40-43] or mind-body exercises[44,45] are important recommendations during the life of an older adult who is exposed to aging-associated physiological/pathological dysfunctions. The use of this form of exercise, Baduanjin training, can be safely used in controlling the elderly' metabolic disturbances and complications.[46,47] Besides its ability to be easily taught by the elderly, this training can be advised by exercise trainers, physiotherapists, health educators, *etc* to improve aging-related metabolic and cognitive consequences.

Limitations of the study

Besides the follow-up to the results, imaging studies of the participants' brains to document objective evidence-based cognitive changes or improvements in response to the Baduanjin exercise are needed in future studies to cover this limitation in our SCH study. Identifying and discussing potential confounding variables (marriage, utilization of leisure times, anxiety, stress, dietary habits, etc.) that could have influenced the results of this study is another limitation that must be faced in future trials.

Conclusion

The results of the adding Baduanjin exercise to the pharmacological course of SCH were encouraging. The 12-week Baduanjin training not only improved SBP, LD-lipo, DBP, TSH, BMI, HD-lipo, TG, and TC but also improved the mild cognitive impairment (assessed by ACEQ-III) in elderly women with SCH.

Ethics approval statement

This SCH trial received the local ethical approval (registration number P.T/REC/012/004294) at Cairo University (Faculty of Physical Therapy).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ali Mohamed Ali Ismail: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mona Mohamed Morsy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Funding source

This study was not funded by any local/international authorities.

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