Euras J Fam Med 2021;10(2):41-8. doi:10.33880/ejfm.2021100201 **Original Research**

The Effect of Vitamin B12, Physical and Cognitive Activity on Idiopathic Forgetfulness

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ABSTRACT

Aim: In this study, we aimed to evaluate the effect of physical activity, vitamin B supplementation and mental activity on cognitive functions in middle-aged individuals with subjective forgetfulness.

Methods: We included 82 people between 40-65 years of age who were admitted to Erciyes University Faculty of Medicine, Family Medicine and Neurology Departments polyclinics with the complaint of subjective forgetfulness between May 2017 and May 2018. General physical examination, blood tests including B12, folic acid level and thyroid functions were performed. In addition to the socio-demographic questionnaire, Beck Anxiety and Beck Depression Scale, Montreal Cognitive Assessment Test, Visual and Verbal Memory Tests were performed. Sixty-eight subjects were randomly allocated to 3 groups as cognitive activity, physical activity and vitamin B supplementation. The physical activity group made a minimum of half-hour brisk walk daily. The cognitive activity group was asked to solve a hooked puzzle every day. Vitamin supplement group used daily vitamin B complex. At the end of the third month, cognitive tests and B12 blood level test were repeated.

Results: Improvement in cognitive functions was found only in the walking group. Long-term visual memory and verbal memory sub-test scores improved significantly in all groups. There were some differences between the groups in terms of verbal memory subtest scores.

Conclusion: In people with forgetfulness, walking, puzzle and vitamin B supplementation seem to have positive effects even after a period of three months in terms of cognitive functions and memory.

Keywords: dementia, cognitive activity, exercise, physical, B vitamins

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Introduction

Thanks to the developments in medicine and other scientific fields, human life is prolonged. Human beings have to face the new problems brought by the elderly population. The changes caused by aging in the human body and diseases that are difficult to treat reached the dimensions that affect not only the elderly individuals but also the family, the environment and even the whole society. Countries have to take into account the elderly population on many issues such as health management, resource use and future cost projections.

According to the World Health Organization 2017 data, it is reported that there are 50 million dementias worldwide and an additional 10 million people are diagnosed with dementia each year. The frequency of dementia is estimated to be between 5-8% among people aged 60 and over. 82 million of people with dementia in 2030; it is predicted that it will be 152 million in 2050. It is estimated that a large part of this increase will depend on the increase in low and medium development countries (1).

According to the 2016 report of the Alzheimer's Society, 5.4 million people in the United States are diagnosed with Alzheimer's Disease (AD). This number is estimated to be more than double in 2050. Today, one person gets this disease every minute. It is fifth in deaths over 65 years old. In 2016, care and health expenditures for people with dementia over 65 are estimated at 236 billion US Dollars (2).

According to the Economic Development and Cooperation Organization 2016 data, the estimated dementia patient in the European Union countries is 9.6 million. This figure is estimated to be 15 million in 2035. This frequency varies between countries. While the prevalence of dementia for Germany and Italy was over 20 per thousand, this figure was below 10 per thousand for Slovakia. This has been associated with the age and demographic structure of the country's populations. For all European Union countries, 1% of the population between the ages of 60-64 and 40% of the population over the age of 90 are reported to be dementia (3).

In this study, it was aimed to evaluate the effects of exercise, B vitamins and mental activities on cognitive functions in middle-aged individuals who have not been diagnosed with dementia but have subjective forgetfulness. We think that the results of the study will provide useful data in developing simple, feasible and inexpensive suggestions for people with risk factors for dementia in primary health care delivery.

Methods

This study started with the approval of Erciyes University Ethics Committee dated 21.04.2017 and numbered 2017-216 and the approval of the Scientific Research Project (BAP) committee's TTU-2017-7456 project number. The study was carried out prospectively in Erciyes University Faculty of Medicine, Erciyes Hospital, Department of Family Medicine. By explaining the purpose and procedure of the study to all patients, the study was carried out in accordance with the Helsinki declaration principles. In addition, informed consent was obtained from the patients.

The study included 82 people between the ages of 40-65 who applied to Erciyes University Faculty of Medicine, Family Medicine and Neurology Department polyclinics between May 2017 and 2018 with subjective complaints of forgetfulness. All patients' history was recorded in terms of date of birth, place of birth, place of residence, occupational information and systemic diseases. General physical examination was performed to the patients. In addition, 8 hours after fasting complete blood count, vitamin B12 level (0-3 months), folic acid level, fasting blood sugar, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), calcium, blood urea nitrogen (BUN), blood tests including creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride, total cholesterol, T3, T4, thyroid stimulating hormone (TSH) level, erythrocyte sedimentation rate (ESR) were performed. Apart from the socio-demographic questionnaire, Beck Anxiety and Beck Depression Scale, Montreal Cognitive Assessment Test (MoCA),

Weschler Memory Scale (WMS), Visual Production Subtest and Öktem Verbal Memory Process Test were applied at the beginning of the study and at the end of the third month.

Beck Anxiety Test and Beck Depression Test were performed to the participants in terms of depression and anxiety disorder that may affect cognitive tests at the beginning and end of the study. Accordingly, individuals above the mild depression level (16<points) were excluded from the study.

Eight different cognitive functions are evaluated with the MoCA: attention and concentration, executive functions, memory, language, visual structuring skills, abstract thinking, computation and orientation. The points are collected after the test is applied to individuals. The highest score that can be obtained from the test is 30. Scores of 21 and above are considered normal.

Patients with depression, diagnosed dementia (AD, vascular dementia), with hypothyroidism, hearing, vision or physical illnesses that make it difficult to comply with the tests and study groups at the end of the preliminary evaluation, patients with psychiatric disease, vitamin B12 below 200 pg / ml was excluded from the study. Fourteen of the participants were excluded in line with the study criteria. 68 people who were eligible for the study were randomly distributed to 3 groups as cognitive activity (n=23), physical activity (n=23) and vitamin supplements (n=22). The physical activity group was asked to take brisk walks, with a minimum of half an hour daily. Patients were asked to record these walks with the pedometer given to increase their motivation and compliance. The source from the cognitive activity group was asked to solve one puzzle per day and bring the puzzles with them at the end of the study. The vitamin supplement group was asked to use one B vitamin complex per day. A monthly communication was established with the participants in terms of the side effect profile and work compliance. At the end of the third month, tests and B12 blood level test were repeated.

Fourteen of the patients included in the study stopped working for various reasons. 54 people completed the study, 19 people from the physical activity group, 17 people from the puzzle group and 18 people from the vitamin group.

Statistical analysis of the data was done in SPSS for Windows program (SPSS for Windows software, version 20.0, SPSS Inc, Chicago, IL). The distribution of the data was evaluated using Shapiro Wilk test. The Kruskal Wallis test, which was used to analyze non-parametric data, was used to compare more than two independent groups. Wilcoxon Test were used to analyze the data of two dependent groups. $p < 0.05$ level was considered statistically significant.

Results

Demographic data are given in Table 1. The average age of 54 people (male = 12, female = 42) who completed the study was found to be 49.7.

Table 1. Gender, education and occupation status

		Group		
		Exercise	Vitamin	Puzzle
Gender	Men	3	3	6
	Women	16	14	12
Educational Level	Illiterate	1	1	0
	Primary School	11	13	11
	High School	3	1	3
	University	4	2	4
Occupation	Employee	4	3	7
	Housewife	10	12	7
	Clerk	5	2	4

There was no significant difference between the study groups in terms of age (p=0.864). It was seen that the participants in the study were mostly women and this was observed in all groups. The educational status of the patients is at primary or after level, except for two people. 10 people are graduates. There was no difference between groups in terms of educational status. In terms of occupational groups, it is noteworthy that the majority of the participants were housewives. There was no significant difference between the groups in terms of fasting blood sugar, thyroid function tests, AST, ALT, ALT, BUN, creatinine, hemoglobin, calcium levels and ESR (Table 2).

Table 2. Study groups' age and blood tests

	Group			p
	Exercise	Vitamin	Puzzle	
	Median (25-75%)	Median (25-75%)	Median (25-75%)	
Age	47 (46-55)	49 (45-52)	51 (42-56)	0.864
FPG (mg/dl)	99 (87-103)	91 (89-97)	91,00 (83-96)	0.224
Hb (g/dl)	13.40 (12.8-14.7)	14 (13.30-14.90)	14.45 (13.80-15.10)	0.128
TSH (µIU/ml)	1.66 (1.36-2.60)	1.64 (1.24-2.29)	1.60 (1.06-2.66)	0.943
T4 (ng/dl)	1.12 (1.03-1.30)	1.20 (1.10-1.33)	1.20 (1.09-1.27)	0.709
Folic acid (ng/ml)	8.1 (6.50-10.00)	9.00 (6.20-10.30)	7.05 (5.60-10.70)	0.977
B12 first (pg/ml)	311 (276-341)	250 (215-289)	342 (205-423)	**0.024**
B12 last (pg/ml)	280 (270-377)	372 (287-519)	322.85 (261-379)	0.106

While there was no difference in folic acid levels at the beginning of the study; B12 levels were significantly lower in the vitamin supplement group (p=0.024). There was no difference between groups in terms of repeated vitamin B12 levels (p=0.106). There was no statistically significant difference between the groups in terms of depression and anxiety scales that may affect cognitive functions at the beginning and end of the study (Table 3).

Table 3. Beck Depression-Beck Anxiety Scales according to groups

	Group			*P*
	Exercise	Vitamin	Puzzle	
	Median (25-75%)	Median (25-75%)	Median (25-75%)	
BECK-D first	8 (4-11)	10 (7-13)	9 (5-11)	0.334
BECK-D last	6 (3-9)	7 (5-10)	7 (4-11)	0.340
BECK-A first	8 (6-11)	10 (9-13)	10 (6-19)	0.196
BECK-A last	6 (3-10)	11 (8-19)	11 (3-21)	0.164

BECKD=Beck Depression, BECKA=Beck Anxiety

At the beginning of the study, there was a significant difference between the groups in terms of MoCA total score (p=0.029) (Table 4).

Table 4. MBDT total scores

		First	Last	p
		Median (25-75%)	Median (25-75%)	
Group	Exercise	21 (16-25)[ab]	23 (17-25)[ed]	**0.049**
	Vitamin	18 (16-23)[a]	19 (17-24)[e]	0.390
	Puzzle	24 (22-27)[b]	26 (23-28)[d]	0.229
	p	**0.029**	**0.011**	

* [a b e d] *Show the statistical difference between the groups*

This difference was statistically significant between the puzzle and vitamin groups (lower than the vitamin group) as a result of binary analysis (p=0.028). It was observed that MoCA total scores increased slightly in all groups at the end of the study. This increase was found to be significant only in the walking group (p=0.049). The significant difference between the vitamin and puzzle groups observed at the beginning of the study continued at the end of the study (p=0.008). There was no significant difference between the groups at the beginning and at the end of the study in terms of instant visual memory test scores (p>0.05). No significant changes were observed in any of the groups at the end of the study (Table 5).

Tablo 5. Difference and change between groups in terms of instant visual memory test

		First	Last	p
		Median (25-75%)	Median (25-75%)	
Group	Exercise	11 (7-12)	11 (7-13)	0.326
	Vitamin	9 (8-12)	10 (6-13)	0.266
	Puzzle	13 (8-13)	13 (12-14)	0.103
	p	0.160	0.054	

While there was no significant difference between the groups at the beginning and end of the study in terms of long term visual memory test scores; at the end of the study, a significant increase was observed in all groups (Table 6). There was no difference between the groups in terms of instantaneous verbal memory scores at the beginning of the study. In the end of study double comparison analysis, vitamin group was found to be statistically lower than exercise group (p=0.042). Instant verbal memory test scores increased significantly in all groups at the end of the study.

Tablo 6. Difference and change between groups in terms of long visual memory test

		First	Last	
		Median (25-75%)	Median (25-75%)	**p**
Group	Exercise	9 (5-10)	10 (6-13)	**0.030**
	Vitamin	8 (3-10)	9 (5-10)	**0.016**
	Puzzle	11 (7-12)	12 (10-14)	**0.042**
	p	0.052	0.062	

At the beginning of the study, a significant difference was found between the groups in terms of verbal memory learning test (p=0.049). Verbal memory learning test scores were lower than the other groups in the vitamin group at the beginning of the study. Verbal memory learning test scores increased significantly in all groups at the end of the study. There was no difference between the groups in terms of verbal memory recall scores before the study. At the end of the study, the vitamin group was found lower than the other groups. Verbal memory recall test scores increased significantly in all groups at the end of the study. During the study, none of the participants had any side effects that would affect their health or compliance with the study.

Discussion

Advances in advancing health technologies and medicine have provided longer life. The increase in the elderly population all over the world has prevented the health problems related to old age from being the problem of only people and institutions working in this field. This global problem has started to play an important role in the health expenditures of countries. In addition, the elderly population has implications for meeting individual needs and rehabilitation processes and the quality of life of their social environment.

Although the pharmacological agents used today have positive effects on the course of the disease, these drugs do not completely stop the decline in cognitive functions and cannot return the loss. In a meta-analysis (n=5149) involving studies comparing cholinesterase inhibitors to placebo in people with mild cognitive impairment, these drugs reduce the risk of cognitive impairment progression to dementia and a low level of effect on healing cognitive scores. However, frequent side effects profile, which are not vital, especially in the gastrointestinal tract, have been observed (4). Drug treatment has various side effects and usage difficulties for patients with dementia. For this reason, it has become a primary goal to detect early signs of dementia and to develop preventive strategies for people at risk. Studies conducted on this subject aimed to control risk factors related to systemic diseases, life changes such as exercise, diet, computer programs or cognitive activities containing various intelligence games, micronutrient supplements, and stop or improve regression in cognitive functions.

Beck Anxiety Test and Beck Depression Test were performed to the participants in terms of depression and anxiety disorder that may affect cognitive tests at the beginning and end of the study. In a systematic review, Gulpers et al. (5) were revealed that anxiety is a risk factor for cognitive decline and dementia. There was no difference between the groups included in the study in terms of these two test scores.

There was no difference in basal blood tests, thyroid function tests and folic acid levels. B12 vitamin levels measured before the study were found to be lower than the other groups only in the group who received vitamin supplements. At the end of the study, it was seen that this difference disappeared. The relationship between B12 deficiency and regression in cognitive functions has been known for a long time. However, it is uncertain exactly through which mechanisms this relationship occurs. B12 acts as a cofactor in the methylation of homocysteine and methyl malonic acid. One of the proposed mechanisms is due to insufficient methylation of homocysteine and an increase in homocysteine levels due to low vitamin B12 levels. Due to high levels of homocysteine, cerebral vascular network damage, brain atrophy and white matter damage occur (6). Supporting this mechanism, the relationship between high homocysteine levels and regression in cognitive functions has been shown in many studies (7,8). In the study of Haan et al. (9), it was stated that serum homocysteine level is an independent risk factor for dementia and non-dementia cognitive disorder. In the same study, high B12 levels were found to be

protective in terms of the risk of homocysteine-related dementia. In a study comparing mild cognitive impairment and AD with healthy control group, low serum B12 and folate levels, high homocysteine levels were found to be associated with mild cognitive impairment and AD (10). In contrast, in a meta-analysis comparing the B vitamin combinations (Folate ± B12, B6 vitamins) with the placebo group in people with mild dementia, a significant decrease in homocysteine levels; cognitive functions evaluated with mini-mental state examination did not improve (11). In our study, serum homocysteine levels were not evaluated.

An increase in MoCA scores was observed in all groups. However, only improvement in physical activity group was found statistically significant (p=0.049). This may be due to the effect of changes in physical activity on cognitive functions in a shorter time. In the SMART study, the effects of resistance exercise, cognitive activity and the combined application of these two on cognitive functions were investigated for 6 months in people with mild cognitive impairment. In the physical activity group, there was a significant improvement in the global cognition at 6 and 18 months compared to the control group. There was no significant difference in the computerized cognitive activity group compared to the control group. Interestingly, it was observed that the combined group achieved less gains in cognitive functions and executive functions than the physical activity group. The effects of these activities on memory were found to be variable (12).

In our study, there was no combined group and control group. Also, repeated tests for the long-term efficacy of our study were not performed. As a result, with a screening test in which cognitive functions were generally discussed, an improvement in cognitive functions was observed in all groups, meaningful only in the walking group, in a period of 3 months.

While there was no difference at the beginning of the study in terms of instantaneous verbal memory and verbal memory recall scores; at the end of the study, it was observed that the vitamin group was significantly lower than the other groups. In one study, it was found that in people with mild cognitive impairment, those with low levels of vitamin B12 (within the normal limit range) had poor learning capacity and recognition performance, regardless of age, education, homocysteine and folate levels. In the same study, the hippocampus structural integrity was shown to be worse in the lower group (13). At the end of the third month, a significant increase was observed in all verbal memory and verbal memory recall scores in all groups.

Lampit et al. (14) conducted a meta-analysis in 2014 (52 studies, n=4885), the effects of home computer programs on cognitive functions in healthy individuals over 60 years of age were examined. Accordingly, a small but statistically significant improvement was observed in all cognitive functions. Similar effects were found for verbal and nonverbal memory. Only attention and executive functions were not changed. The difference in the puzzle group was interpreted as the effect of cognitive exercise on the related memory function was slower or weak.

When the verbal memory tests are analyzed in general, significant improvement in the subtest scores of all study groups draws attention. Improvement in some subtests occurred differently between the groups. For example, in terms of instantaneous verbal memory and verbal memory recall scores, the vitamin group showed less improvement than the exercise group. Cheng et al. (15), in their study, they examined the effect of leisure activities on cognitive functions in people with mild dementia. In Tai Chi (balance exercise) and Mahjong (traditional puzzle) groups, MoCA and some short-term memory scores improved significantly compared to the control group that performed simple handicrafts (3 months). After the study, it was observed that it continued more prominently in the 6th and 9th month evaluations. In our study, the level of memory and cognitive changes to continue in long-term follow-up was not evaluated.

Conclusion

There was a difference between the groups at the beginning and end of the study in terms of cognitive functions. Vitamin group scores were significantly

lower at the beginning and end of the study compared to the puzzle group. The difference in the MoCA scores of the vitamin group may be related to the low B12 vitamin level of this group prior to the study. This screening test, in which the cognitive functions were handled in general, showed a significant improvement only in the walking group in a period of three months, it was observed. All three life changes were found to have positive effects on some components of visual memory.

In terms of instantaneous verbal memory and verbal memory learning, verbal memory recall scores, there was a significant increase in all groups at the end of the third month. People with simple amnesia had positive effects in terms of cognitive functions and memory in a period of three months. Improvement in cognitive function was found to be significant only in walking group. The memory function improved in various levels in all groups. Some differences were observed between the groups in terms of memory subtest scores.

In people with forgetfulness, walking, puzzle and vitamin B supplementation seem to have positive effects even after a period of three months in terms of cognitive functions and memory.

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