

EFFECTS OF ACETYLCHOLINESTERASE INHIBITORS ON NUTRITIONAL STATUS IN ELDERLY PATIENTS WITH DEMENTIA: A 6-MONTH FOLLOW-UP STUDY

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Abstract: *Objectives:* Nutritional status is one of the factors that affects disease progression, morbidity and mortality in elderly patients with dementia. The present study aimed to evaluate the effect of acetylcholinesterase inhibitor (AChEI) therapy on nutritional status and food intake in the elderly. *Design, setting and participants:* Newly diagnosed patients with dementia, who underwent comprehensive geriatric assessment (CGA) and were followed at regular intervals, were retrospectively evaluated. A total of 116 patients, who began to receive AChEI therapy and completed 6-month follow-up period under this treatment, were enrolled in the study. *Measurements:* Socio-demographic characteristics and data on comorbidity, polypharmacy, cognitive function, depression, activities of daily living and nutritional status (weight, Body Mass Index (BMI), Mini Nutritional Assessment (MNA)-Short Form) were recorded. *Results:* The mean age of the patients was 78.0±8.9 years. There was no significant difference between baseline and 6-month BMI, weight and MNA scores of dementia patients who received AChEI therapy ($p>0.05$). With regard to the relation between changes in BMI, weight and MNA on the 6th month versus baseline, and donepezil, rivastigmine and galantamine therapies, no difference was determined ($p>0.05$). However, no worsening in food intake was observed (κ : 0.377). When the effects of each AChEI on food intake were compared, food intake in rivastigmine treated patients was not decreased as much as it was in galantamine or donepezil treated patients ($p<0.05$). *Conclusion:* AChEI therapy has no unfavorable effect on nutritional status or weight in elderly patients with different types of dementia, but it seems that food intake is better in those treated by rivastigmine patch.

Key words: Dementia, elderly, nutrition, acetylcholinesterase inhibitor, weight, body mass index.

Introduction

Malnutrition and cognitive deficit are two major geriatric syndromes, and recently it has been dwelled on the probability of these two syndromes to be in close relation with each other independent of aging (1, 2). There are several mechanisms blamed for this relation: one of these is the occurrence of repeated actions and behavioral disorders due to episodic memory and impairment in attention, resulting in increased energy loss in patients with dementia (3). Another one is the involvement of sensation of smell and taste and impaired swallowing function due to cholinergic deficit (4, 5). Cognitive deterioration in the elderly affects daily functional status and instrumental activities, which results in disability, dependence and decreased food intake. Food intake is affected significantly by chewing and swallowing difficulties, and decreased appetite in these patients (6). In the light of all these likely mechanisms, the risk of malnutrition can arise even from the prodromal period of dementia (7). Although the mechanisms that cause malnutrition in different types of dementia aren't known exactly, it has been reported that increased eating and swallowing problems are more common among patients with Lewy bodies dementia, compared to Alzheimer's Disease (8).

Nearly half of the elderly patients with dementia in the population have the risk of malnutrition (8) which also increases cognitive impairments and the incidence of

behavioral disorders, and decreases functionality and quality of life in these patients (9, 10). As a result, a vicious cycle appears between malnutrition and cognitive deficit.

Acetylcholinesterase inhibitors (AChEI) are the first-line drugs in the treatment of mild to moderate Alzheimer's Disease and Lewy Body Dementia (11). Although for vascular dementia (VaD), the results of studies are confusing, AChEIs may have modest beneficial effects on cognitive symptoms of VaD (12). In addition, AChEI can be suggested for the treatment of memory and executive impairment due to rare dementia, such as Corticobasal Degeneration (13). Appetite and weight loss can be seen due to gastrointestinal side effects such as nausea, vomiting and diarrhea, particularly in the beginning of the treatment (14). However, there is limited number of studies upon the effect of long-term AChEI therapy on nutritional status, of which the results are conflicting (14), and the effect of AChEI therapy on food intake, including appetite, digestive, chewing and swallowing functions, isn't known clearly.

Therefore, this study was aimed to demonstrate the effect of AChEIs on food intake and nutritional assessment parameters in the elderly over the course of 6-month follow-up period.

Materials and Methods

Patients

Files of 208 dementia patients, who had undergone comprehensive geriatric assessment between June 2013 and October 2014 in the Aging Brain and Dementia Unit and had been followed at regular intervals, were reviewed. A total of 116 dementia patients, who had complete file records and met the eligibility criteria, were enrolled in this retrospective study. The study was consonant to the Declaration of Helsinki and was approved by the local ethics committee.

Inclusion criteria

Patients with Dementia: Patients, who had not been diagnosed with dementia before and not receiving any anti-dementia drug, donepezil, rivastigmine, and galantamine were diagnosed with dementia according to the DSM-IV-TR diagnostic criteria (15). In addition, each of these patients was evaluated via Magnetic Resonance Imaging. After making the diagnosis, the patients were treated with a flexible 4 weekly donepezil dosage titration regimen up to 10 mg/d, rivastigmine transdermal dosage titration regimen up to 9.5 mg/d, and galantamine dosage titration regimen up to 24 mg/d. Patients who had completed 6-month follow-up period with this treatment were included in the study.

Exclusion criteria

- Age < 65 years
- Patients that developed hypersensitivity and severe gastrointestinal intolerance, which required withdrawal of drug during the dose titration period for each AChEIs.
- Patients with dementia had no indication for AChEI (such as Frontotemporal dementia)
- Patients that had acute confusional state, psychotic attack (schisoaffective disorder, etc.), or treatment-resistant major depressive disorder during evaluation
- Patients with the history of diseases that might seriously impair their general health such as acute cerebrovascular event, gastrointestinal bleeding, sepsis, acute renal insufficiency, acute coronary syndrome, acute hepatic insufficiency, and acute respiratory failure, or history of intensive care unit admission
- Patients with -from stage 1 to stage 4- solid or hematological cancers or hyperthyroidism that might effect nutritional status; with gastrointestinal diseases such as inflammatory bowel disease or malabsorption syndrome; with chronic liver disease or end-stage renal insufficiency
- Patients with swallowing disfunction caused by any reason, such as cerebrovascular disease sequela or neuromuscular disease
- Patients that were being fed through a nasogastric catheter or that had undergone percutaneous endoscopic gastrostomy (PEG)
- Patients receiving drugs that might affect nutrition and

appetite (chemotherapeutics, megestrol acetate, corticosteroids, mirtazapine etc.)

- Patients with any nutritional intervention
- Patients abusing substance

Comprehensive Geriatric Assessment (CGA) (16)

Socio-demographic characteristics of the participants including age, gender, education and living environment were recorded. Data in patient files were examined to see whether their medical history reveals presence of hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, peripheral vascular disease, hyperlipidemia, cerebrovascular disease, depression, osteoporosis and polypharmacy. In addition, comorbidities were assessed using GIC (Geriatrics index of comorbidity) (17). Cognitive functions of the patients were evaluated by Cognitive State Test (COST) (18) and Mini-Mental State Examination (MMSE) (19).

In addition, scores of the Cornell Dementia Depression Scale (CDDS) (20), basic and instrumental Activities of Daily Living (BADL, IADL respectively) indexes, and Zarit Burden Scale (ZBS) were also recorded for each patient (21-23).

To calculate body mass index (BMI), height was measured to the nearest centimeter (cm) and weight was measured to the nearest half-kilogram (kg) with the same stadiometer. Mini Nutritional Assessment (MNA)-Short form was performed in all patients; 12-14: well-nourished; 8-11: risk of malnutrition; and ≤ 7 : malnutrition (24). Food intake status of the patients was assessed according to the answers given by patient attendants to the question "Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?" found in MNA-Short form (24). Patients were divided into three groups according to the answers "severe decrease in food intake", "moderate decrease in food intake" and "no decrease in food intake".

Laboratory findings

Certain laboratory tests were routinely done to assess biochemical, metabolic and nutritional status of the patients in our center (25). For this purpose, hospital laboratory recordings were also reviewed for complete blood count, C-reactive protein (CRP), kidney and liver functions, albumin and cholesterol levels, free triiodothyronine (T3), free thyroxin (T4), thyroid stimulating hormone (TSH), and vitamin B12 and folic acid levels. All of these biochemical tests were done using Diagnostic Modular Systems autoanalyzer (Roche E170 and P-800).

Follow-up

CGA was re-performed at the end of the 6th month. They were divided into three groups according to the 6th-month cognitive test scores: those with improvement (an increase in MMSE score was ≥ 1), with no change in MMSE, and with worsening (a decrease in MMSE score was ≥ 1).

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Statistical analysis

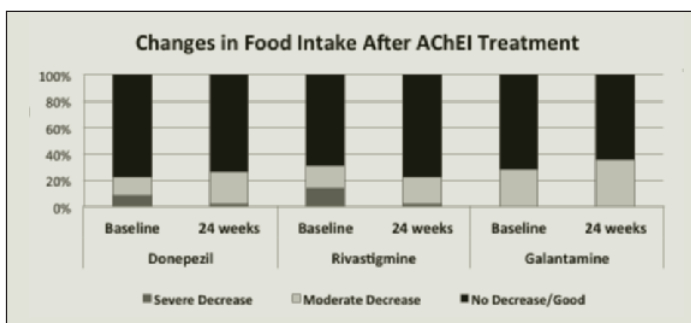
Statistical analyses were done using SPSS 15.0 (SPSS Inc.) Continuous variables were expressed as mean ± standard deviation. Kolmogorov-Smirnov test was used to analyze continuous variables in terms of suitability of normal distribution. Continuous variables with normal distribution were analyzed by paired Sample t-test, whereas continuous variables without normal distribution were analyzed by Wilcoxon test. Whether there is significant change between the visits performed at baseline and on the 6th month was analyzed using paired t-test or Wilcoxon Signed Rank test. Changes between the visits was calculated by the [(before treatment - after treatment) / before treatment] formula. Differences in proportions were analyzed using chi-square test. The relation between AchEI use and the changes between visits was assessed by Kruskal-Wallis Test. Changes between the visits in the patient groups that improved, not changed and worsened at the end of 6th month, which were determined based on cognitive test scores, were analyzed by Kruskal-Wallis Test. Kappa consistency test was used for the changes in food intake. A probability <0.05 was considered significant.

Results

Baseline characteristics of patients are demonstrated in Table 1. Of the 116 patients, 100 had been diagnosed with Alzheimer-type Dementia, 9 had been diagnosed with Lewy Body Dementia, 7 had been diagnosed with Vascular Dementia, and 2 had been diagnosed with Corticobasal Degeneration.

Figure 1

Changes in Food Intake After Acetylcholinesterase Inhibitors Treatment



The patients were similar in terms of baseline and 6th-month laboratory findings, scores of MMSE, COST and BADL index, and the results of CDDS and ZBS (p >0.05). It was determined that only IADL significantly improved on the 6th month versus baseline (p <0.05). There was no difference in terms of BMI, weight and MNA scores (p >0.05) (Table 2). With regard to the relation between the changes in BMI, weight and MNA score on the 6th month versus baseline and the use of donepezil, rivastigmine and galantamine, no relation

was determined (p >0.05) (Table 3). According to the changes in food intake, any change in favor of decreasing was not observed in our patients (kappa: 0.377). Whilst 10.4% of the patients had serious loss of food intake, 16.8% had moderate loss of food intake and 78.8% had no change/good food intake before treatment, these rates were 2.1%, 25.0% and 72.9%, respectively on the 6th month of therapy. When the effects of each AchEI on food intake were compared, food intake in rivastigmine treated patients was not decreased as much as it was in galantamine or donepezil treated patients (p <0.05) (Figure 1).

Table 1
Characteristics Of Patients

Patients with Dementia (n:116)	
Age (years)	78.0 ± 8.9
Gender (female/male)	65/51
Education (years)	4.71 ± 4.40
Living circumstances (%)	
• With the spouse	69 (58.7)
• With family caregiver	42 (36.2)
• With caregiver	4 (3.4)
• In nursing home	2 (1.7)
GIC	1.8 ± 0.2
Comorbidities n (%)	
HT	67 (57.8)
DM	29 (25.0)
CAD	16 (13.8)
CHF	8 (6.9)
PVD	5 (4.3)
CVD	9 (7.8)
OP	22 (19.0)
HL	16 (13.8)
Depression	37 (31.9)

CAD: coronary artery disease; CHF: congestive heart failure; CVD: cerebrovascular disease; DM: diabetes mellitus; GIC: Geriatrics index of comorbidity; HL: hyperlipidemia; HT: hypertension; OP: osteoporosis; PVD: peripheral vascular disease

Furthermore, we found that mean changes in BMI, MNA score and weight, were not different after 6-month AchEI treatment in those patients with worsened (increase in MMSE score was ≥ 1) (n=21), unchanged (no change in MMSE) (n=52), and improved cognition (decrease in MMSE score was ≥ 1) (n=43) (p >0.05).

Discussion

The present study showed that AchEI therapy has no unfavorable effect on nutritional parameters in the elderly

Table 2
Comparison of baseline and 6th-month findings in patients with dementia

	Patients with Dementia (116)		
	Baseline	6th month	p value
Number of drugs	5.23 ± 3.54	4.68 ± 2.02	0.51
<i>Laboratory Values</i>			
Hgb (g/L)	12.68 ± 1.43	12.63±1.43	0.85
CRP (mg/dl)	0.76±0.82	0.81±0.87	0.09
Creatinine (mg/dL)	0.96±0.25	1.0±0.29	0.06
Albumin (g/L)	3.99±0.30	3.99±0.29	0.82
TSH (uIU/mL)	1.74±1.75	1.67±1.47	0.59
Free T3 (pg/mL)	3.12±0.91	3.14±0.83	0.63
Free T4 (ng/dL)	1.01±0.21	1.08±0.15	0.87
Total cholesterol (mg/dL)	187.4±50.2	188.9±50.3	0.69
LDL cholesterol (mg/dL)	125.56±40.13	126.81±37.21	0.99
HDL cholesterol (mg/dL)	49.24±11.80	51.76±13.63	0.02
Vitamin B12 (pmol/L)	455.62±234.21	451.82±152.17	0.84
Folic acid (ng/mL)	8.24±3.10	8.17±4.86	0.83
<i>Geriatric Assessment</i>			
MMSE	18.14±5.42	18.89±5.11	0.16
COST	19.41±5.09	20.76±4.99	0.54
BADL	84.63±17.12	85.87±17.61	0.10
IADL	6.12±5.08	7.04±4.78	0.03
CSDD	13.37±6.11	12.23±7.54	0.21
ZBS	19.67±9.16	21.25±10.83	0.27
<i>Nutritional Assessment</i>			
BMI (kg/m ²)	27.21±4.84	26.97±4.55	0.14
Weight (kg)	68.19±14.12	67.62±13.70	0.07
MNA	10.62±2.36	10.84±1.89	0.43
• MNA>11	54 (46.6)*	52 (44.8)*	0.74**
• 8≤MNA≤11	49 (42.2)*	53 (45.7)*	
• MNA≤7	13 (11.2)*	11 (9.5)*	

BADL: Basic activities of daily living (0 [worst]-100 [best]), BMI: Body Mass Index; COST: Cognitive State Test (0 [worst]-30 [best]); CSDD: Cornell Scale for Depression in Dementia (0 [best]- 38 [worst]); HDL: High Density Lipoprotein; IADL: Instrumental activities of daily living (0 [worst]-17 [best]); LDL: Low Density Lipoprotein; MMSE: Mini-Mental State Examination (0 [worst]-30 [best]); MNA: Mini Nutritional Assessment (0 [worst]-14 [best]); TSH: Thyroid Stimulating Hormone; ZBS: Zarit Burden Scale (0 [worst]-88 [best]); * n (%); ** p value for comparison of the patients according to MNA groups

patients with dementia and that food intake may be improved in the patients treated with rivastigmine.

The percentage of malnutrition and the risk of malnutrition in elderly patients, who have been newly diagnosed with dementia, were 11.2% and 42.2%, respectively in this study. High percentage risk of malnutrition is consistent with the results of previous studies (7). However, in our study the prevalence of malnutrition was found to be higher. It may be because that the prevalence of malnutrition is already high in our country (%13), due to the low socioeconomic status of our country and low educational level of the patients (25, 26).

There are numerous studies that demonstrate the close relation between cognitive and functional deficit, and malnutrition in patients with dementia (1). Although AchEIs are not curative, they are able to stabilize memory and delay functional reduction (27); however, it remains unclear how the long-term usage of these drugs affects nutritional status, which is one of the factors that significantly influence disease progression. It is reported that AchEIs may cause weight loss by increasing cholinergic activity in the gastrointestinal system and causing nausea and diarrhea; however, this information is limited to the case reports (29). In the studies in which the patients have been followed only for weight loss, it was observed that there is significant weight loss in the patients receiving AchEI compared to placebo (29) but the risk decreases after the 3rd month of cholinergic therapy (30). In addition to those studies, the present one also showed no weight loss in the patients on the 6th-month visit, although it seems as if there is a tendency to weight loss. In this study, different from the previous ones (30, 31); it was demonstrated that AchEI therapy has no unfavorable effect on nutrition in the elderly by MNA. Up to now, there is limited number of studies that used MNA for this subject (9, 32, 33). The results of those studies whose primary aim is not to determine the effect of AchEI on nutrition are conflicting. In one of them, Cortes et al. reported no significant change in MNA in a one-year follow-up study (33), although they reported worsening in MNA in another 18-month study (32). In another one, a 6-month study conducted by Vellas et al., it was determined that MNA has been favorably influenced by AchEI therapy in the patients with the risk of malnutrition while MNA has been unfavorably influenced in well-nourished dementia patients (9). However, those studies did not offer any details to the comorbidities and laboratory parameters, the number of the malnourished patients before treatment, and the type and dose of the AchEI

Table 3
Mean Changes in Nutritional Characteristics of the Patients according to Acetylcholinesterase inhibitors

	Donepezil (48)	Rivastigmine (48)	Galantamine (20)	p value
BMI	0.01 ± 0.47	0.00 ± 0.53	0.00 ± 0.39	0.45
Weight	0.11 ± 0.04	0.00 ± 0.06	0.00 ± 0.06	0.47
MNA	-0.02 ± 0.26	-0.15 ± 0.49	-0.03 ± 0.15	0.67

BMI: Body Mass Index; MNA: Mini Nutritional Assessment

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(21, 22). In this study we were able to exclude all the factors affecting cognitive functions and nutritional status, since the comorbidities and laboratory parameters of the patients were detailed. Therefore, the present study is one of the rare studies that evaluate clearly the effects of AchEIs on nutrition in elderly patients with dementia. It was previously reported that repetitive tasks and restlessness occur in patients with dementia due to episodic memory and impaired attention and that they use a large amount of energy in trying to complete the activities of daily living (34-36). It might be the reason for malnutrition in such patients (3), but this study didn't demonstrate any interaction between nutritional parameters and cognitive changes at the end of the 6th month. In fact, it demonstrated that AchEIs do not influence nutrition over this mechanism. This suggests that other factors might be responsible.

Another important aspect of the present study is the evaluation of food intake over the course of treatment period. Both inflammatory effects of AchEIs over cholinergic pathways and their ability to improve sensation of smell and taste due to increase in acetylcholine concentration in olfactory mucosa and taste buds may explain improvement in appetite in patients with dementia (5, 37). Improvement in swallowing function due to increased acetylcholine concentration may be another reason (38). However, the reason that there is no decrease in food intake with transdermal rivastigmine versus other AchEIs may be associated with better tolerability and lower gastrointestinal side effects (39, 40). In addition to ability of AchE inhibition, rivastigmine might have also contributed to the improvement in appetite and swallowing over above-mentioned mechanisms by inhibiting butyrylcholinesterase (4). All these hypotheses can be illuminated by the studies that would be performed in the future. The fact that nutrition has not been improved enough despite favorably influenced food intake suggests that studies with longer follow-up period are needed.

The present study has some limitations. First, it is a retrospective study, so we depend on the data collection in the past. Second, it has low sample size, which limits its statistical significance. Third, a comparison with any control groups could not be performed due to lack of dementia patients that had not been treated or received placebo. A placebo-controlled study is the ideal way to assess the effect of AchEIs on nutritional parameters, but such a study is difficult to perform because of ethical reasons. Fourth, effects of AchEIs on different types of dementia could not be evaluated because of limited number of patients with non-Alzheimer Dementia. Last one, the effect of behavioral disorders, such as apathy, hallucinations, agitations, on nutrition was not investigated. In addition, using specific screening tools, such as Appetite Assessment Questionnaire and Eating Behavior Scale, could improve the impact of the present study in order to evaluate food intake in elderly patients with dementia (41, 42).

In conclusion, the risk of malnutrition is quite high in Turkish elderly patients with dementia. We concluded that in patients with different types of dementia who tolerated different

AchEIs treatments, AchEIs did not only have any negative effects on nutritional status but also did not decline weight during 6 months. Furthermore, food intake may be better in patients with dementia treated by rivastigmine patch.

Conflict of interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper. We would like to acknowledge Dr. Hulya Ellidokuz for help in statistical evaluation of the study.

Ethical standards: This study was approved by the Local Ethics Committee of Dokuz Eylul University (2014/37-11).

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