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MEMANTINE EFFECTS ON INSULIN RESISTANCE IN ALZHEIMER'S DISEASE

Mehdi Maghbooli[1], Hossein Chiti[2], Nafiseh Jabbari Daneshvar[2], Maryam Jameshorani[2], Masoud Asadi-Khiavi[3,4,*]

[1]Department of Neurology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

[2]Zanjan Metabolic Disease Research Center, Zanjan University of Medical Sciences, Zanjan, Iran.

[3]Zanjan Applied Pharmacology Research Center, Zanjan University of Medical Sciences, Zanjan, Iran.

[4]Department of Pharmacotherapy, School of Pharmacy, Zanjan University of Medical Science, Zanjan, Iran.

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***Correspondence for Author**
Dr. Masoud Asadi-Khiavi
Department of Pharmacotherapy, School of Pharmacy, Zanjan University of Medical Science, Zanjan, Iran.

ABSTRACT

Background: Insulin resistance is a risk factor for Alzheimer's disease (AD). Deficit in insulin metabolism can lead to the deterioration of the clinical course of AD. Furthermore, Memantine have revealed remarkable clinical efficacy. This study was designed to study of insulin resistance and Memantine relationship in AD. **Patients and Methods:** Fifty six AD patients were enrolled in this study at Zanjan Vali-e-Asr university hospital. They were randomly divided in two groups based on receiving Memantine or placebo in associated with standard therapies for both groups. AD diagnosis was confirmed using the standard criteria. Treatment continued for one month. Anthropometric parameters, serum Triglyceride, Total Cholesterol, HDL, fasting insulin and Blood Sugar were measured before and after treatment. Insulin resistance was calculated using the HOMA (Homeostasis Model Assessment) index. **Results:** There was no correlation between HOMA index variations and Memantine consumption; however, patients aged 70 years and older had lower insulin resistance. Significantly decrease in hip and waist circumference was observed in the Memantine using group. The HOMA index and severity of AD did not show any

significant correlation. **Conclusions:** One month Memantine therapy did not significantly provide alteration on insulin resistance level. It seems to further studies are needed for this issue.

KEYWORDS: Insulin resistance, Memantine, Alzheimer's disease.

INTRODUCTION

AD as a progressive and irreversible brain disorder is the most common cause of dementia and involves the cognitive domains (Memory, attention, language, visuo-spatial planning and decision making), character, thought content, perception and behavior. The disease is the fourth leading cause of death in western countries and also is the seventh major cause of death in the world.[26,17] It is estimated that approximately 2.5 million people over 65 years old have AD's disease in the United States and it is anticipated to be tripled in the next 40 years.[1,22] Aging and Apolipoprotein E4 genotyping are two known risk factors for Alzheimer's disease.[24,20] Other factors such as family history, female gender, education, trauma, high blood pressure and diabetes may have role in etiology of the disease.[5,15,23,25] Insulin resistance is a common problem in type II diabetes mellitus which may appear several years before hyperglycemia. Insulin resistance is one of important factors in AD and hypoglycemic drugs using have some benefits on it. Memantine as an adamantine derivative agent inhibits N-methyl-D-aspartic acid receptors (NMDA) without any excessive effect on receptor function and works as neuroprotective agent as well.[8,13] NMDA receptors are found in the hippocampus and cerebral cortex frequently. These receptors are involved in rapid synaptic transmission at the central nervous system. NMDA receptors are modulated by Insulin through phosphorylation of the Insulin receptor substrate p53 and consequent subcellular events. This study was designed to evaluation of Memantine effects on insulin resistance in according to mentioned inhibitory role on NMDA receptors as well as Insulin resistance role in the pathogenesis of AD.[11,18]

PATIENTS AND METHODS

Fifty six cases of well-known Alzheimer's disease from nursing homes of Zanjan and Khoramdareh cities were enrolled in this study. These patients did not have any history or evidence of insulin resistance or diabetes before. A history of diabetes (type one or two), fasting plasma glucose of 126mg/dl or higher, use of steroids and drugs with affect on insulin resistance, BMI $\geq$ 40kg/m2, any non-Alzheimer's dementia and secondary cognitive impairment, history of allergy to the Memantine, liver failure, kidney failure and seizure

were mentioned as exclusion criteria. Diagnostic and statistical manual of mental disorders (DSM-IV) and the national institute of neurological and communicative disorders and stroke - AD and related disorders association (NINCDS-ADRDA) criteria were used to diagnosis confirmation. AD severity was categorized as mild, moderate and severe based on these criteria. Baseline blood samples were obtained for fasting plasma glucose, total cholesterol, triglycerides, high density lipoproteins and insulin level evaluation as well. Insulin resistance was determined by the Homeostasis Model Assessment (HOMA) method.[9,7] Anthropometric parameters including height, weight, waist and hip circumferences were obtained too. The patients were randomly assigned to receive oral Memantine (10mg) and placebo daily for at least one month duration in intervention and placebo groups respectively. In according to the Rogawski and colleagues study, Memantine serum therapeutic levels are achieved within 21 days of drug consumption.[6,14,21] Memantine was provided from Osvah pharmaceutical company. Accurate use of medicines by patients was monitored by an observer (caregivers or family members) through checklist Mark. On the end of one month treatment, fasting glucose, insulin and lipid profiles and anthropometric measurements were determined and insulin resistance was calculated using HOMA indices. Cases with HOMA index greater than or equal to 2.1 were known as insulin resistant. A descriptive analysis was used to analyze the data, using SPSS software version 19 (Chicago IL, SPSS Inc). Demographic and baseline characteristics were expressed as frequency. Percentage was used for nominal variables and Mean ± SD for continuous variables. Normal distribution of data was determined by the kolmogrov-smirnov test. Comparison of quantitative values between the two groups with normal distribution was performed using independent sample t test and Mann-Whitney test was performed for others. Paired t test and Wilcoxon test were used to compare variables before and after treatment in each group with and without normal distribution, respectively. P values ≤ 0.05 were considered to be statistically significant. Detailed design of the study was explained to the patients and their families and/or legal guardians. The written informed consent was obtained from all subjects and their legal executors. Ethical permission was obtained, all information remained confidential and mural aspects of study were accepted in details of the plan adopted in the Medical Ethics Committee of Zanjan University of Medical Sciences. The Limitations of study including lack of timely referral of patients for plasma glucose testing as well as cases address and telephone number alteration and finally incomplete or improper consumption of drugs by patients were considered at the beginning of trial as well.

RESULTS

Of the 56 enrolled subjects, 22(3.39%) were male and 34(7.60%) female. Sex distribution in Memantine group was as 50-50; while in the placebo group 62.8% were male and 47.1% female. The mean age of the study population was 52.11 ± 4.74, with the maximum age of 117 years and the minimum age of 54 years. Mean anthropometric measurements were within normal range in both groups. Mean BMI of patients was 23.2 ± 4.8 in Memantine group and 22.7±3.7 in the placebo group (normal range). Detailed anthropometric variables of the patients are presented in Table1.

Table 1- Comparison of Anthropometric values between Memantine and Placebo groups [a].

	Control group (Placebo consumption)			Intervention group (Mementine consumption)		
	Post Treatment	**Pre Treatment**	***P_{value}**	**Post Treatment**	**Pre Treatment**	***P_{value}**
Weight	52.7 ± 11.5	52 ± 11.12	0.161	54.9 ± 11.78	55 ± 11.82	0.326
Height	151.85 ± 8.71	151.85 ± 8.72	--	154 ± 7.82	154 ± 7.82	--
Waist circumference	72.35 ± 11.67	72.53 ± 11.63	0.202	74.5 ± 11.83	74.71 ± 11.81	0.031
Hip circumference	79.07 ± 10.37	79.25 ± 10.57	0.096	83.6 ± 11.06	83.89 ± 10.99	0.032
BMI	22.75 ± 3.33	22.79 ±3.33	0.167	23.20 ± 4.87	23.21 ± 4.87	0.326

[a] *Data are presented as Mean ± SD.*

**P_{value}* *lower than 0.05 was considered as statistically significant.*

In intervention group there was significant difference in waist and hip circumferences before and after treatment with a decrescendo pattern (P value = 0.031 and P value = 0.032 respectively). The mean values of body weight decreased after treatment with Memantine, but in comparison with pretreatment, the difference was not significant.

Table 2- Comparison of mean serum levels of biochemical indicators before and after treatment between placebo and Memantine groups [a].

	Intervention group (Mementine consumption)			Control group (Placebo consumption)		
	Post Treatment	**Pre Treatment**	***P_{value}**	**Post Treatment**	**Pre Treatment**	***P_{value}**
TG	127.2 ± 39.3	116.4 ± 34.9	0.03	133.8 ± 46.9	123.2± 43.8	0.185
Cholesterol	182 ± 29.8	175.9 ± 28.5	0.93	195 ± 51.4	184.3 ± 54.1	0.240
HDL	43.4 ± 9.1	41.3 ± 6.6	0.11	44.7 ± 8.3	41.77 ± 9.1	0.124

[a] *Data are presented as Mean ± SD.*

**P_{value}* *lower than 0.05 was considered as statistically significant.*

Also, there was no significant difference between the variables before and after treatment with placebo. According to disease severity scale, 11 patients (3.39%) of Memantine group and 20 patients (4.71%) in the placebo group suffered from mild AD. Fourteen patients (50%) of Memantine group and 8 patients (6.28%) in the placebo group had moderate and only 3(7.10%) patients in Memantine group had severe Alzheimer's disease. Indicators such as serum triglycerides and HDL cholesterol were not significantly different before and after treatment with Memantine (Table 2). The mean HOMA index before treatment with Memantine was 0.99 versus 2.1 after treatment. Despite increase in the index after treatment with Memantine, this difference was not significant (P value = 0.81). The difference of mean serum level of indicators and anthropometric variables were studied pre-and post-treatment in the both Memantine and placebo groups (Table 3).

Table 3- Comparison of treatment induced changes in the mean of the variables between placebo and Memantine groups [a].

Variable	Groups	Change values	*P_{value}
TG variation	M	41.9 ± 10.7	0.98
	P	17.1 ± 10.6	
Total Cholesterol variation	M	26.6 ± 6	0.56
	P	32.4 ± 10.6	
HDL variation	M	6.7 ± 2	0.54
	P	5.9 ± 3	
Weight variation	M	0.18 ± 0.03	0.56
	P	0.26 ± 0.07	
Waist circumference	M	0.49 ± 0.21	0.80
	P	0.72 ± 0.17	
Hip circumference variation	M	0.58 ± 0.25	0.63
	P	0.54 ± 0.17	
BMI variation	M	0.08 ± 0.01	0.54
	P	0 ± 0.03.12	
HOMA-Index	M	3.4 ± 0.267	0.22
	P	6.1 ± 2.75	

[a] *Data are presented as Mean ± SD.*

**P*$_{value}$ *lower than 0.05 was considered as statistically significant.*

M: Memantine and P: Placebo.

It should be noted that height changes were not comparable due to the lack of change by treatments. Further comparisons showed that there was no significant difference between two groups, especially in HOMA-Index and insulin resistance.

Table 4 - Comparison of HOMA index variations in according to age groups before and after Memantine using [a].

Age groups (years)		HOMA index	*P_{value}
50-59	Before treatment	0.62 ± 0.35	0.490
	After treatment	3 ± 2.46	
60-69	Before treatment	1.46 ± 1.29	0.747
	After treatment	1.70 ± 1.05	
70-79	Before treatment	1.76 ± 1.53	0.010
	After treatment	0.39 ± 0.13	
> 80	Before treatment	0.63 ± 0.39	0.014
	After treatment	0.48 ± 0.19	

[a] *Data are presented as Mean ± SD.*

**P*$_{value}$ *lower than 0.05 was considered as statistically significant.*

Subgroup analysis according to gender, age and anthropometric parameters indicated that the differences were not significant, except in two subgroups of the Memantine treated patients who had age above 70 years and BMI less than 18.5, so that mean HOMA index showed significant changes after treatment.

Table 5- Comparison of changes in HOMA indices based on BMI categories before and after treatment with Memantine [a].

Body Mass Index		HOMA Index	*P_{value}
< 18.5 (underweight)	Before treatment	1.07 ±0.93	0.026
	After treatment	0.40 ± 0.14	
18.5 ≤ BMI ≤ 24.9 (normal)	Before treatment	0.57 ± 0.33	0.299
	After treatment	1.01 ± 0.65	
25 ≤ BMI ≤ 29.9 (overweight)	Before treatment	0.53 ± 0.12	0.813
	After treatment	0.44 ± 0.16	
≥ 30 (obesity)	Before treatment	3.29 ± 1.67	0.474
	After treatment	2.42 ± 1.93	

[a] *Data are presented as Mean ± SD.*

**P*$_{value}$ *lower than 0.05 was considered as statistically significant.*

DISCUSSION

The results showed that waist and hip circumference of patients were significantly decreased after treatment with Memantine. Because such studies have not been done previously on the effects of Memantine on measures of obesity, a study like the current one will reveal new pharmacological effects of this combined regimen. However, in this study, other anthropometric variables such as weight and BMI did not change significantly after

treatment. Diabetes and insulin resistance are known as risk factors for Alzheimer's disease; many studies have shown that cerebral neurons of patients with Alzheimer-type dementia have impaired glucose metabolism and some degree of insulin resistance. In a study on mice with Alzheimer's disease, diet-induced insulin resistance increased Amyloidosis. These findings suggest that insulin resistance can cause Alzheimer's disease or at least exacerbate it. Cerebral glucose utilization and some enzymatic activity participate in glucose metabolism are disturbed in Alzheimer's disease.[10,19] Some previous studies have hypothesized that insulin dysfunction has a pathologic link with sporadic Alzheimer's disease.[3,4] It seems that alteration in the glucose and insulin metabolism is one of the mechanisms that may be used to treat Alzheimer's disease. There is a relationship between glucose metabolism and beta-Amyloid and cholinergic transmission in animal models, which expresses the relationship between cerebral cortical cholinergic activity and glucose metabolism.[2,16] In our study, Like Isik et al study, the HOMA index was used to measure peripheral insulin resistance. The results also showed that there are a significant relationship between insulin resistance and severity of the disease. The higher HOMA indices were associated with more severe disease. This means that the degree of insulin resistance is associated with the clinical severity of dementia symptoms and is consistent with previous studies. Lisbon in an extensive study over 14 years followed diabetic patients and eventually concluded that diabetes is a major risk factor for Alzheimer's disease and dementia. They observed that a high percentage of subjects were affected by the dementia at the end of their lives. Since impairment of the insulin resistance can occur months or years former than diabetes, its proper and exact control can be effective in reducing or postponing symptoms of dementia. Treatment with Memantine did not influence significantly on the laboratory parameters such as triglycerides and HDL cholesterol in comparison with placebo group. Also, in the Memantine group, these values did not show any meaningful alteration before and after treatment. In Ahmet Turan Isik study, clinical symptoms of Alzheimer's disease was significantly improved using Rivastigmine, but did not demonstrate any significant effect on insulin resistance. He also showed the beneficial effects of Galantamine in cognition without any role in reducing insulin resistance previously.[12] Strength of the current study, compared to other studies was the use of placebo despite similar results. Also we reviewed anthropometric and laboratory measures and their changes with treatment. Many studies have examined the Memantine efficacy on Alzheimer's brain cells and some of them; have proved its role in the brain glucose metabolism.

CONCLUSION AND SUGGESTIONS

Memantine treatment did not lead to a reduction in peripheral insulin resistance. This drug may have some effects in improving insulin and glucose metabolism in brain neurons. Complementary studies with longer period of treatment and follow up, like as Rivastigmin study can be useful. It is also suggested that higher doses of Memantine be used for future studies; and follow up studies (e.g. case - control studies) be designed to investigate the relationship between Memantine and insulin resistance. It is predictable that such studies will be very conducive if be done in a longer time period for evaluation of therapeutic and side effects profile.

ETHICAL CONSIDERATIONS

The research followed the tenets of the Declaration of Helsinki; detailed design of the study was explained to the patients and their families and/or legal guardians. The written informed consent was obtained from all subjects and their legal executors. Ethical permission was obtained, all information remained confidential and mural aspects of study were accepted in details of the plan adopted in the Medical Ethics Committee of Zanjan University of Medical Sciences. Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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