

## A DIFFERENT VIEW TO OLDER DIABETICS: MANAGEMENT OF TREATMENT ACCORDING TO COGNITIVE FUNCTIONS

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### Abstract

**Background and aims.** Diabetes Mellitus is a chronic systemic disease which has multiple complications and the presence of these complications affects the management of disease. It is also important to consider cognitive functions when managing the treatment of older diabetics. In this study, we aimed to make proposals for the appropriate drug choice to preserve cognitive functions in elderly diabetics. **Material and methods.** A total of 270 older diabetic patients were reviewed. Possible risk factors of cognitive impairment were investigated. Correlation analysis was performed between MMSE and GDS, age, HbA1c, duration of diabetes. **Results.** Sulfonylurea (adj. OR: 2.33, %95 CI: 1.11- 4.90) and insulin treatment (adj. OR: 3.79, %95 CI: 1.56-9.21) were found associated with increased risk of cognitive impairment. In addition, there was a negative correlation between MMSE and GDS ( $r: -.129, p<0.05$ ). **Conclusion.** We suggest that insulin and sulfonylureas should be used with caution in those with cognitive impairment.

**key words:** Diabetes mellitus; cognitive impairment, dementia

### Background and aims

Diabetes Mellitus (DM) is a chronic systemic disease with significant morbidity and mortality, which is very common in the community. It has multiple complications, both microvascular and macrovascular, and the presence of these complications affects the management of disease [1].

The purpose of DM treatment is to prevent acute and chronic complications. In order to prevent diabetes complications, the targets of glycosylated hemoglobin (HbA1c), fasting

glucose and postprandial glucose levels were determined and aimed to reach these targets [1]. The management of older diabetic patients whose complications were not developed and not fragile is not different from that of young counterparts. However, when treating patients with chronic complications, targets may be kept more flexible to prevent hypoglycemia and its adverse consequences [1]. It is also important to consider cognitive functions and functional status when managing the treatment of older diabetics, especially those who are fragile.

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Cognitive impairment is an important health problem affecting elder patient's life quality. It is also common in elderly diabetic patients. Cognitive impairment may already exist or may develop during the course of the diabetes. The relationship between diabetes regulation and cognitive impairment has been investigated in previous studies. Recent studies have shown that HbA1c is associated with cognitive functions and functional status [2-4]. In addition to diabetes regulation, some studies have examined the association of antidiabetic drugs with cognitive impairment [5-11]. However, previous studies are inadequate in the management of elderly diabetics and new studies are needed. In this study, we aimed to make proposals for the appropriate drug choice to preserve cognitive functions in elderly diabetics, especially those with cognitive impairment, by investigating the relationship between cognitive impairment and antidiabetic drugs.

### **Material and methods**

After the study was approved by the Ethics Committee of the Ankara University, the medical records of the patients who applied to Ankara University School of Medicine at the geriatric outpatient clinic in 2017 were evaluated. Patient information was reached from patient polyclinic file records. Patients whose antidiabetic drugs were changed in last one year excluded from study. 270 remaining patients were included in the study. Firstly, general informations such as age, gender and drugs especially antidiabetics of the participants were recorded. In addition, their comprehensive geriatric tests including Katz daily living activities, Lawton-Brody instrumental activities of daily living, mini nutritional assessment short form (MNA), mini mental state examination (MMSE), Yesavage geriatric depression score (GDS) and laboratory tests (HbA1c, LDL

cholesterol, HDL cholesterol) were noted. Patients with MMSE score below 24 were considered to have cognitive impairment, and GDS score higher than 5 were considered to have depression.

Statistical analysis were performed using Statistical Package for Social Sciences (SPSS) for Windows 20.0 (IBM SPSS Inc., Chicago, IL). Data were analyzed by normality and homogeneity of variance tests. Males and females were compared in terms of mean values of age, geriatric test scores and laboratory parameters by performing independent t-test. Results were given as mean  $\pm$  standard deviation and p value  $<0.05$  were considered significant. Possible risk factors of cognitive impairment were investigated by binary logistic regression analysis. Diabetic drugs, HbA1c, duration of diabetes, microvascular complications, the presence of coronary artery disease (CAD) and cerebrovascular accident (CVA), depression and hypoglycemia were examined as possible risk parameters. Results were given as adjusted odd ratio (%95 confidence interval) and p value  $<0.05$  were considered significant. Also, the relationship between MMSE and GDS, age, sex, HbA1c, duration of diabetes were investigated by Pearson correlation analysis. Correlation coefficients were noted as Pearson's r and p value  $<0.05$  were considered significant.

### **Results**

A total of 270 diabetic patients, 71 male and 199 female, participated in the study. The mean age of the participants were  $72.75 \pm 6.13$  year (females vs. males respectively;  $72.88 \pm 6.24$ ,  $72.35 \pm 5.84$ ) and the mean HbA1c of participants were  $7.85 \pm 1.83$  %. The mean value of MMSE test scores of males were significantly higher than females; mean value of depression scores and HDL cholesterol levels were significantly lower ( $p < 0.05$ ) ([Table 1](#)). Of the

patients 212 were metformin, 75 were insulin, 72 glinid, 9 were acarbose, 6 were glitazon users. were sulfonylurea, 55 were dpp-4, 29 were

**Table 1.** Geriatric tests and laboratory parameters of study population.

	Mean ± Standard Deviation			P value
	Male (N:71)	Female (N:199)	Total (N:270)	
Age, year	72.35 ± 5.84	72.88 ± 6.24	72.75 ± 6.13	Ns
Duration of diabetes, year	12.30 ± 8.45	12.68 ± 8.38	12.58 ± 8.38	Ns
Katz ADL	5.76 ± .96	5.77 ± .93	5.77 ± .94	Ns
Lawton-Brody IADL	7.04 ± 1.88	7.19 ± 1.89	7.15 ± 1.88	Ns
MMSE	25.83 ± 4.11	24.59 ± 4.31	24.92 ± 4.29	0.033*
GDS	2.69 ± 2.75	3.88 ± 3.16	3.57 ± 3.10	0.005*
HbA1c , %	7.94 ± 1.79	7.82 ± 1.84	7.85 ± 1.83	Ns
LDL cholesterol, mg/dl	109.22 ± 35.63	116.79 ± 40.82	114.80 ± 39.60	Ns
HDL cholesterol, mg/dl	43.49 ± 10.99	51.50 ± 18.15	49.40 ± 16.92	<0.001*

\**p*<0.05; ADL: activities of daily living; IADL: instrumental activities of daily living; MMSE: mini mental state examination; GDS: geriatric depression scale; LDL: low density lipoprotein; HDL: high density lipoprotein

**Table 2.** Cognitive impairment risk factors.

	OR (%95 CI)	Adjusted OR (%95 CI)	P Value
Insulin	1.64 (1.07- 2.51)	3.79 (1.56 – 9.21)	.003*
Metformin	.85 (.53- 1.37)	1.53 (.69 - 3.39)	Ns
Sulfonylurea	1.09 (.70- 1.69)	2.33 (1.11 – 4.90)	.026*
DPP-4 inhibitor	.95 (.57- 1.58)	1.34 (.65 - 2.80)	Ns
Akarboz	1.19 (.39- 3.62)	1.48 (.32 – 6.86)	Ns
Glitazon	1.29 (.30- 5.45)	1.87 (.28 - 12.64)	Ns
Glinid	.64 (.29- 1.39)	.84(.29 – 2.40)	Ns
Age, year	1.08 (1.04-1.11)	1.07 (1.02 - 1.13)	.005*
Sex(female)	1.95 (1.24- 3.08)	1.71 (.83- 3.49)	Ns
CVA	1.86 (.61- 5.64)	2.61 (.51 – 13.31)	Ns
HbA1c, %	1.04 (.93- 1.16)	.91 (.74 - 1.10)	Ns
Depression (GDS>5)	2.01 (1.16- 3.49)	1.59 (.88 – 2.90)	Ns
CAD	.86 (.53- 1.41)	.86 (.41 - 1.83)	Ns
Duration of diabetes, year	1.00 (.98- 1.03)	.95 (.94 – 1.02)	Ns
Microvascular complications	1.56 (1.00- 2.43)	1.30 (.64 - 2.66)	Ns
Hypoglycaemia	1.14 (.65- 1.99)	.62 (.24 – 1.59)	Ns

\**p*<0.05; DPP-4:dipeptidyl peptidase-4; CVA: cerebrovascular accident; CAD: coronary artery disease; OR: odds ratio; CI: confidence interval

Patients were examined for risk factors of cognitive impairment. Advanced age (adj. OR: 1.08, %95 CI: 1.04-1.11) sulfonylurea (adj. OR: 2.33, %95 CI: 1.11- 4.90) and insulin treatment (adj. OR: 3.79, %95 CI: 1.56-9.21) were found associated with increased risk of cognitive impairment ([Table 2](#)).

Correlation analysis revealed a negative correlation between age and MMSE ( $r: -.200, p<0.05$ ). In addition, there was a negative correlation between MMSE and GDS ( $r: -.129, p<0.05$ ). In contrast, there was no correlation between MMSE with duration of diabetes and HbA1c ([Table 3](#)).

**Table 3.** Correlation analysis between MMSE and age, duration of diabetes, HbA1c, GDS.

		Age	Duration of diabetes	HbA1c	GDS
MMSE	Pearson correlation	-.200	.051	.025	-.129
	Sig. (2-tailed)	.001*	.402	.678	.034*
	N	270	270	270	270

\* $p<0.05$ ; MMSE: mini mental state examination; GDS: geriatric depression scale

### Conclusion

DM is an important health problem that causes morbidity and mortality in the community [1]. The goal of DM treatment is to prevent complications, also the presence of complications should also taken into account in determining treatment goals [1]. In addition, cognitive and functional status of elderly diabetics may complicate diabetes management. However, there are few studies to determine the importance of cognitive and physical performance [5-11]. Considering effects of glucose regulation and diabetic drugs on cognitive and physical performance may contribute to the maintenance of the quality of life in older diabetics. In the present study, we examined risk factors for cognitive functions in older patients with DM. Also we investigated which antidiabetic drugs are appropriate to preserve cognitive functions.

In our study, male diabetic patients were found to have lower depression scores and higher MMSE scores than women. This may be due to the fact that our older women are less educated and have fewer social experiences due to the patriarchal society structure in our developing country. With the increase education

level of women, this difference may disappear in the future.

When the diabetic patients were examined in terms of the risk factors of cognitive impairment, it was concluded that advancing age increased cognitive impairment. Many other studies suggesting that age progression leads to cognitive impairment supports this finding [12-14]. This result indicates that cognitive impairment should be considered in elderly diabetics.

We found that HbA1c levels were not associated risk of cognitive impairment. In addition, a large number of studies have shown that there is a relationship between high levels of HbA1c and poor cognitive status, whereas heterogeneous results has been reported between the cognition and HbA1c levels [15-20]. These mixed findings suggest a complex interaction between the blood glucose regulation and cognitive functions. Although there was no association between the presence of episodes of hypoglycemia and cognitive impairment in our study, episodes of hypoglycaemia occurring in tight regulation may be the cause of this complex interaction. Contrary to our results Bruce et al. have shown that there may be a relationship between hypoglycaemia and cognitive

dysfunction [21]. This difference finding may be due to hypoglycemic episodes that could not be detected due to neuropathy in our study.

In our study, the presence of depression was not associated with increased risk of cognitive impairment. However, mini-mental test scores were found to be negatively correlated with depression score. Although depression was not found to be a risk factor for cognitive impairment, the decrease in cognitive test scores as depression scores increased, suggesting that the severity of depression affects cognition rather than the presence of depression. There are also many studies showing that depression has affected cognition [22-24].

We found that insulin and sulfonylurea treatment were associated with risk of cognitive impairment and the other antidiabetic drugs were not associated with cognition. There are some studies examining the relationship between cognitive functions and antidiabetic drugs. Trento et al. found that depression worsened and low MMSE scores were associated with insulin treatment [5]. In contrast, a study in Alzheimer's patients has shown that insulin use may be effective in slowing cognitive impairment [6]. Also, there are many studies showing the relationship between cognitive impairment and increased insulin levels [25-27]. As a result, it is possible that sulfonylurea and exogenous insulin administration may lead to cognitive impairment by increasing insulin levels. We found that metformin and dpp-4 were not associated with cognitive impairment risk. There are several studies examining the effect of metformin and ddp-4 on cognitive function. Recent studies showing that the use of metformin is related to poor cognitive function, while some studies have reported the opposite [7,8]. On the other hand, there are studies showing improvement in cognitive functions with sitagliptin and

vildagliptin [9,10]. However in a review study conducted in June 2017, it was concluded that no specific treatment was prevented from cognitive impairment [11]. More comprehensive prospective studies are needed to explain this confusing situation in previous studies.

Current studies are insufficient for older diabetics management and new studies are needed. Our study examines the relationship between diabetes and its treatment with cognitive functions and provides an insight into the cognitive functions of diabetic patients. We think that the findings of our study may guide clinicians in terms of preservation of cognitive impairment. However, there were some limitations of our study. First, this study was designed retrospectively. Hence, we could not able to reach all data. Also the lack of drug doses were another limitation of the study. Despite these limitations, the results of our study may contribute to the management of elderly diabetes

In conclusion, our results suggest that insulin and sulfonylureas may lead to cognitive impairment. Based on this finding we suggest that insulin and sulfonylureas should be used with caution in those with cognitive impairment.

**Conflict of interest.** All authors declare that they have no conflict of interest.

**Compliance with ethical standarts.** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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