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# Short-Term Effects of Metformin and Diabetic Diet on Cognitive Functions in Newly Diagnosed Type 2 Diabetes Mellitus Patients

## Yeni Tanı Tip 2 Diabetes Mellitus Hastalarında Metformin ve Diabetik Diyetin Bilişsel Fonksiyonlara Kısa Dönem Etkisi

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## ABSTRACT

**Aim:** We aimed to investigate the effects of metformin or dietary treatment on cognitive functions in newly diagnosed Type 2 Diabetes Mellitus patients.

**Material and Methods:** Our study was designed prospective. The study included 64 healthy controls and 72 newly diagnosed Type 2 Diabetes Mellitus patients. Metformin treatment for thirty-seven patients and dietary treatment for thirty-five patients were administered by a single endocrinologist. Rey Auditory Verbal Learning Test, Rey Complex Figure Test, Digit Span Test and Trail Making Test for all patients were performed at the time of diagnosis and at the sixth-month of the treatment by a blinded neurologist.

**Results:** At the time of diagnosis, we observed that verbal memory scores in the diabetes group were significantly lower than healthy controls (p= 0.03 in dietary, p= 0.044 in metformin group). Sixth- month evaluation revealed that dietary treatment improved only immediate verbal memory scores (p= 0.041). Metformin treatment, along with verbal memory scores, also significantly improved visual spatial memory (p= 0.014) and processing memory and executive functions (p= 0.036 and p= 0.001).

**Conclusion:** We determined a statistically significant improvement in verbal memory, visual spatial memory and processing speed & executive function scores with metformin treatment, while dietary treatment improved only verbal memory scores.

**Key Words:** Diabetes mellitus, Metformin, Memory, Trail making test, Neuropsychological tests

## ÖZ

**Amaç:** Çalışmamızda yeni tanı Tip 2 Diabetes Mellitus hastalarında, metformin veya diyet tedavisinin bilişsel işlevler üzerindeki kısa dönem etkilerini araştırmayı amaçladık.

**Gereç ve Yöntemler:** Çalışmamız prospektif olarak tasarlandı. Çalışmaya 64 sağlıklı kontrol ve 72 yeni tanı Tip 2 Diabetes Mellitus hastası dahil edildi. Otuz yedi hasta için metformin tedavisi ve otuz beş hasta için diyet tedavisi tek bir endokrinoloji uzmanı tarafından başlandı. Tüm hastalar için Rey İşitsel Sözel Öğrenme Testi, Rey Kompleks Figur Testi, Sayı Dizisi Testi ve İz Sürme Testi, tanı anında ve tedavinin altıncı ayında tedaviye kör bir nöroloji uzmanı tarafından yapıldı.

**Bulgular:** Sözel bellek skorlarının tanı anında diabet grubunda, sağlıklı kontrollerden anlamlı derecede düşük olduğunu gözlemledik (diyet p= 0.03, metformin p= 0.044). Altıncı ay değerlendirilmesinde, diyet tedavisinin sadece anlık sözel bellek skorlarını anlamlı iyileştirdiği görüldü (p= 0.041). Metformin tedavisi, sözel bellek skorları ile beraber ayrıca görsel uzamsal belleği (p= 0.014), işlem belleği ve yürütücü fonksiyonları (p= 0.036 ve p= 0.001) anlamlı düzeyde iyileştirmiştir.

**Sonuç:** Yeni tanı Tip 2 Diabetes Mellitus hastalarında metformin tedavisi ile sözel bellek, görsel uzamsal bellek ile işlem hızı ve yürütücü işlev skorlarında istatistiksel olarak anlamlı düzeyde iyileşme tespit edilirken, diyet tedavisi ile sadece sözel bellek skorlarında iyileşme gözlenmiştir.


**Anahtar Sözcükler:** Diabetes mellitus, Metformin, Hafıza, İz sürme testi, Nöropsikolojik test

## INTRODUCTION

There has been a significant increase in the incidence and prevalence of Type 2 Diabetes Mellitus (T2DM), particularly in individuals over 65 years of age, due to the prolonged lifespan, decreased physical activity and increased obesity (1). In the literature, T2DM is mostly associated with peripheral complications such as nephropathy, neuropathy, and retinopathy, but its effect on cognitive functions has not been adequately addressed (1). It has been reported that T2DM causes slow progressive changes in the brain (2). The negative effects of T2DM on cognitive functions have been reported in many clinical and experimental studies (3-5) and it has been further shown that it is associated with Alzheimer's Disease (AD) (6, 7). Type 3 DM was first used for AD patients with decreased tau protein, which is regulated by insulin and insulin-like growth factor 1 (IGF-1) (8). Relationship between T2DM and cognition may be associated with macro and microvascular changes, T2DM-associated changes, such as impaired glucose metabolism, chronic inflammation, hyperinsulinemia, insulin resistance, or oxidative stress, cardiovascular risk factors such as coexisting hypertension (HT), coronary artery disease (CAD), and risk factors such as dietary habits and reduced physical activity (9). Furthermore, oxidative stress, mitochondrial dysfunction, advanced glycosylation end products (AGEs), apolipoprotein E (ApoE) processing, distortion in cholesterol metabolism and central nervous system (CNS) insulin signaling are present in the pathogenesis of both T2DM and AD (10). Insulin resistance and decreased insulin levels are thought to contribute to the pathogenesis of AD by decreasing the level of acetylcholine (11).

The risk of dementia in patients with T2DM is 1.5-2 times higher than the healthy population (11-13). Cognitive decline is a stage between normal aging and dementia (14). Both T2DM and dementia have a high socioeconomic burden. Therefore, great importance to identify any cause or risk factor that may lead to the development of dementia based on the common pathogenesis of these two diseases and to determine an appropriate treatment. A study within the United States citizens has predicted that deferment of the onset of dementia by two years will decrease the number of patients with dementia to 890,000 after 50 years (15). Therefore, the appropriate treatment of T2DM seems to be an effective option for delaying the onset of dementia.

Metformin is the most preferred drug in the treatment of T2DM (9). Metformin reduces the blood glucose levels by decreasing hepatic glucose output and increasing insulin-stimulated glucose uptake in skeletal muscle and adipocytes (16). Apart from reducing the blood glucose levels, it is currently thought that metformin has a potential therapeutic effect on solid organ cancers such as colorectal, breast and pancreas and on diseases such as cardiovascular disease, AD and obesity (17). Metformin has a direct effect on CNS by crossing the blood-brain barrier (18) and inhibits neuronal apoptosis (19-21).

Lifestyle changes and diabetic diets are the first step treatments for each patient with T2DM. The high glycemic dietary has been shown to cause increased cerebral amyloid deposition (22). Diabetic diet has been reported to regulate DM-induced cognitive deficits and increase learning and memory capacity (23).

In the current literature, there is no consensus on the effects of low glycemic dietary on cognitive functions in adults with poor blood glycose regulation (24, 25).

There are many studies evaluating the relationship between T2DM and cognitive functions (3-7). To the best of our knowledge, there are only a few prospective studies about the effects of different treatment protocols on cognitive functions for T2DM patients (18, 26, 27) .

We hypothesized that we would achieve better cognitive scores within a six-months period with metformin or dietary treatments for the newly diagnosed T2DM patients compared to baseline scores.

## MATERIALS and METHODS

The study was conducted after obtaining the approval of the Baskent University institutional review board (Approval Code: KA10/81) and informed consents from all participating patients. The patients were excluded from the study owing to thyroid disfunction, malignancy, renal or hepatic insufficiency, having neurological or psychiatric diseases that affected the cognitive functions and lost to follow-up visits. Patients, who have comorbid diseases other than diabetes and using chronic medications due to these diseases, were also excluded. Besides, the patients, who have been treated with other antidiabetic drugs except metformin, were excluded from the study. A total of 72 adult patients with newly diagnosed T2DM, who met the study criteria were reviewed prospectively. There were 37 patients in metformin group and 35 patients in dietary treatment group.

Patients, whose 1) a 75-g oral glucose tolerance test with a 2-h value of 200 mg/dL or more, 2) a random plasma glucose of 200 mg/dL or more with typical symptoms of diabetes, or 3) a fasting plasma glucose of 126 mg/dL or more on more than one occasion were diagnosed as T2DM (28). Thyroid dysfunction, depression, chronic obstructive pulmonary disease, liver or kidney failure were excluded from the study in the diabetes and control group, since these diseases would affect the cognition. Patients were evaluated by a single endocrinologist and metformin or diabetic diet therapy was initiated considering the patients' socio-economic status, metabolic status and patient compliance. Individuals without systemic disease and chronic drug use were included in the control group.

The metformin treatment was begun with 1000 mg./day in metformin group and according to blood glucose levels of the patients in the follow-up period, the metformin dosage was increased to a maximum of 3000 mg/day when necessary. In the dietary group, the calorie amount of the diabetic diet was calculated as 20 calories / day for each kilogram of ideal weight as has been described in the study of Bayraktar (29).

The duration of education of all participants (5-8 years, 9-11 years, 12-16 and more than 16 years) were evaluated. The Neurocognitive tests were applied to all patients at the time of diagnosis and at the sixth- month of treatment period by an expert neurologist, who was blinded to diabetic treatment protocols. Rey Auditory Verbal Learning Test (RAVLT) was used to evaluate short- and long-term verbal memory (30), Rey Complex Figure Test (RCFT) was used to evaluate visual-spatial memory (31), forward and backward Digit Span Test (DST) were used to evaluate working memory and attention (32), Trail Making Test (TMT) Part A and B were used for processing speed and executive function (30). For both tests (TMT-A and TMT-B) completion time was recorded. In the control group, there were a total of 64 healthy adults. The same cognitive tests were applied to all healthy controls for once. Higher scores obtained from RAVLT, RCFT and DST tests indicate a better cognitive status. In TMT-A and TMT-B tests, the test completion time was evaluated and the shorter duration indicates better cognitive status. Pairwise comparisons of all groups in terms of cognitive test were performed before treatment.

Statistical analysis was performed using MedCalc®v11.0.1 (Ostend, Belgium) package software. Sample size was calculated accepting type 1 error level as 0.05 and power of the study as 0.80. By accepting the effect size as 0.8, the total sample size was calculated to be at least 52 models. Shapiro-Wilk test was used to determine whether continuous parameters such as neurocognitive tests were normally distributed. Normally distributed descriptive data were expressed as mean and standard deviation. Non-normally distributed data were expressed as median and percentages. Categorical data such as gender was expressed as numbers and percentages. Chi-square analysis was used to analyze the relationships between categorical variables and disease groups. In the comparison of patient groups in terms of the mean parameter values, Student's t-test was used for the normally distributed parameters, whereas the Mann Whitney U test was used for non-normally distributed data. In the comparison of the differences between the mean neurocognitive test scores before the treatment and mean neurocognitive test scores at the sixth-month, paired samples t-Test was used for normally distributed data and Wilcoxon signed-rank test was used

for the non-normally distributed data. In the comparison of patient groups and control group in terms of the mean parameter values, ANOVA test was used for the normally distributed parameters, whereas the Kruskal Wallis test was used for non-normally distributed data. Tukey's HSD (honestly significant difference) and the LSD (least significant difference) tests were used for the pairwise comparison of groups. Furthermore, correlation coefficients were also calculated to test the relationships between neurocognitive tests.

## RESULTS

The mean age was 49.59 ± 6.1 in control, 51.6 ± 6.5 in dietary group and 50.78 ± 6 in metformin groups. The ratio of female patients was 83.8% (n=31), 77.1% (n=27), and 73.4% (n=47) in metformin, dietary, and control group, respectively. There was no statistically significant difference between study groups in terms of mean age (p= 0.28), gender distributions (p= 0.24) and the duration of education (p= 0.056).

Pairwise comparisons, mean and standard deviations of the groups at the time of the diagnosis in terms of verbal and visual spatial memory tests were given in Table 1.

No statistically significant differences were observed between the groups at the time of diagnosis in terms of forward and backward digit span (p= 0.599 and p= 0.940), and TMT parts A & B (p= 0.333 and p= 0.651).

Time-dependent changes of verbal and visual spatial memory scores, simple attention & working memory and processing speed & executive function of dietary group were given in Table 2 and 3, respectively.

**Table 1.** Pairwise comparisons, mean and standard deviations of the groups at the time of diagnosis in terms of verbal and visual spatial memory tests.

| | Tests | Control | Dietary | Metformin | P |
|---|---|---|---|---|---|
| | | Mean-/+SD | Mean-/+SD | Mean-/+SD | |
| Verbal Memory | RAVLT IMMEDIATE RECALL | 6.67 ± 2.09 | 5.83 ± 1.38$_{a}$ | 5.89 ± 1.81$_{a,b}$ | 0.042* |
| | RAVLT DELAYED RECALL | 10.58 ± 2.59 | 9.77 ± 2.44 | 9.46 ± 2.83 | 0.092 |
| Visual Spatial Memory | RCFT IMMEDIATE RECALL | 22.3 ± 7.17 | 22.26 ± 6.65 | 19.93 ± 6.63 | 0.212 |
| | RCFT DELAYED RECALL | 21.5 ± 7.35 | 20.81 ± 6.45 | 19.2 ± 5.65 | 0.267 |

**a.** difference compared to the control group, **b.** difference compared to dietary group, *statistically significant

**Table 2.** Comparison of time dependent changes of verbal and visual spatial memory scores in dietary group.

| | Dietary | Without Treatment | After Treatment | P |
|---|---|---|---|---|
| | | Mean-/+SD | Mean-/+SD | |
| Verbal Memory | RAVLT IMMEDIATE MEMORY | 5.83 ± 1.38 | 6.69 ± 2.49 | 0.04* |
| | RAVLT DELAYED RECALL | 12 ± 2.33 | 12.06 ± 2.23 | 1.00 |
| Visual Spatial Memory | RCFT IMMEDIATE RECALL | 22.26 ± 6.65 | 22.8 ± 6.42 | 0.74 |
| | RCFT DELAYED RECALL | 20.81 ± 6.45 | 20.8 ± 6.21 | 0.08 |

*statistically significant

**Table 3.** Comparison of time-dependent changes of simple attention & working memory and processing speed & executive function in dietary group.

| | Dietary | Without Treatment | | After Treatment | | P |
|---|---|---|---|---|---|---|
| | | Median | IQR | Median | IQR | |
| Simple Attention & Working Memory | FORWARD DIGIT SPAN | 6 | 4 - 7 | 6 | 5 - 7 | 0.77 |
| | BACKWARD DIGIT SPAN | 4 | 3 - 5 | 4 | 3 - 5 | 0.283 |
| Processing Speed & Executive Function | TMT A | 52 | 40 - 65 | 50 | 39 - 60 | 0.069 |
| | TMT B | 97 | 75 - 133 | 100 | 79.5 - 120 | 0.08 |

**IQR:** Interquartile range

Time-dependent changes of verbal and visual spatial memory scores, simple attention & working memory and processing speed & executive function of metformin group were given in Table 4 and 5, respectively.

## DISCUSSION

The most important finding of our current study was at the end of the six-month treatment period the statistically significant improvement of the verbal memory, visual-spatial memory, processing speed and executive functions in metformin group, and also increased verbal memory scores in dietary group.

There has been a significant increase in the incidence and prevalence of T2DM, particularly in individuals over 65 years of age (1, 33). The risk of dementia in patients with T2DM is 1.5-2 times higher than the healthy population (11-13). In the current literature, there are many studies, which investigated the effect of T2DM on cognitive functions in humans and animals (3-7, 34). However, there is only a few prospective studies about the effects of T2DM on cognitive functions and the results of these studies are controversial (9, 26).

We aimed to evaluate the effects of dietary or metformin treatment on cognitive functions in newly diagnosed T2DM patients, prospectively. Besides, we compared the cognitive functions of T2DM patients to healthy adults at the time of diagnosis.

In the current literature, there is no consensus on the effects of low glycemic dietary on cognitive functions in adults with poor blood glycose regulation (24, 25). The high glycemic dietary has been shown to cause increased cerebral amyloid deposition (22) and diabetic diet has been reported to regulate DM-induced cognitive deficits and increase learning and memory capacity (23). Prospective studies investigating the effects of diet on cognition in T2DM are limited (9, 26).

Metformin is the most widely used drug in the treatment of T2DM (9). Metformin has a direct effect on central nervous system (CNS) by crossing the blood-brain barrier (18). Metformin positively affects the hippocampal amyloid-β accumulation by reducing tau phosphorylation and activating the atypical Protein kinase C (PKC) and Csk-binding protein (CBP) pathway and it further positively affects the cognition by inhibiting neuronal apoptosis (19-21). In most of the studies, metformin use in patients with T2DM has been reported to reduce the risk of dementia and cognitive impairment (13, 18). In an in vitro study by Gupta et al., AD-like tau phosphorylation, amyloid-β and neurofibrillary tangles were observed in insulin-resistant neuroblastoma cells and

**Table 4.** Comparison of time dependent changes of verbal and visual spatial memory scores in metformin group.

| | Metformin | Without Treatment | After Treatment | P |
|---|---|---|---|---|
| | | Mean-/+SD | Mean-/+SD | |
| Verbal Memory | RAVLT IMMEDIATE MEMORY | 5.89 ± 1.81 | 6.61 ± 1.91 | 0.0074* |
| | RAVLT DELAYED RECALL | 9.46 ± 2.83 | 9.97 ± 2.99 | 0.192 |
| Visual Spatial Memory | RCFT IMMEDIATE RECALL | 19.93 ± 6.63 | 22.25 ± 6.57 | 0.0143* |
| | RCFT DELAYED RECALL | 19.2 ± 5.65 | 21.22 ± 6.21 | 0.014* |

*statistically significant

**Table 5.** Comparison of time-dependent changes of simple attention & working memory and processing speed & executive function in metformin group.

| | Metformin | Without Treatment | | After Treatment | | P |
|---|---|---|---|---|---|---|
| | | Median | IQR | Median | IQR | |
| Simple Attention & Working Memory | FORWARD DIGIT SPAN | 6 | 5 - 7 | 6 | 5.25 - 7 | 0.124 |
| | BACKWARD DIGIT SPAN | 4 | 3 - 5 | 4 | 3 - 5 | 0.532 |
| Processing Speed & Executive Function | TMT A | 57 | 42.5 - 76.5 | 54 | 42 - 70 | 0.036* |
| | TMT B | 108 | 84 - 146.5 | 99 | 80 - 137.75 | 0.001* |

*statistically significant, **IQR:** Interquartile Range

these changes have been shown to decrease with the use of metformin (35). Metformin treatment has been shown to improve executive function in non-diabetic patients with mild cognitive impairment or mild dementia due to AD (36). In contrast to these studies, Chen et al. reported that metformin increased the amyloid-β formation by activating AMPK and therefore, triggered the AD (37). In a study by Thangthaeng et al. including old male mice, metformin was reported to affect the spatial memory and visual acuity negatively (38). There are also studies compatible with this finding showing that patients with T2DM using metformin have a high risk of developing neurodegenerative diseases including Parkinson's disease and AD (39, 40). Moore et al. also reported lower Mini Mental Test (MMT) scores in patients with T2DM using metformin, however, this association was not significant after they adjusted their analysis for Vitamin B-12 level (41).

Our study results revealed that verbal memory scores and processing speed & executive functions have been negatively affected at the time of diagnosis in newly diagnosed T2DM patients. However, only the verbal memory scores were statistically significant. In a study of Saczynski et al, similar to our study results, lower verbal memory scores were obtained in undiagnosed T2DM patients compared to healthy adults and the difference was statistically significant (4). In our study, impaired verbal memory scores, due to exposure to hyperglycemia from the onset of diabetes to the time of diagnosis, improved statistically significant at the end of the six months of metformin or dietary treatment (p= 0.007 and p= 0.041, respectively). At the end of the six-months of follow-up period of our study, we observed a statistically significant increase of verbal memory scores in metformin group. Similar to our results, in a study of Herath et al., the increased verbal memory scores were obtained in metformin group during the four-year follow-up, however the results differed no statistically significance (9). In contrast to our study results, at the end of the thirty-six weeks of follow-up period by Abbatecola et al., significantly lower verbal memory scores were determined in dietary or metformin groups (26). We think that the reason for obtaining different results in the study of Abbatecola et al. could be due to the inclusion of only T2DM patients with mild cognitive impairment and inadequate compliance of patients to applied dietary treatment.

In our study at the time of diagnosis, visual spatial memory results, which evaluated with RCFT immediate and delayed recall tests, in the newly diagnosed T2DM patient group were not statistically significant when compared to the control group (p= 0.21 and p= 0.26, respectively). RCFT immediate and delayed recall test results in dietary group revealed no statistically significant difference at the end of the follow-up period (p= 0.74 and p= 0.88, respectively), although in metformin group, the difference was statistically significant (p= 0.014 and p= 0.014, respectively). Wennberg et al. found no statistically significant association between metformin treatment and visual spatial memory scores in T2DM patients (27). The reason for the different results in the Wennberg's study could be that the median diagnosis of diabetes was 6.6 years (27). To the best of our knowledge, there is no study in the current literature, which investigate the effects of metformin or dietary treatment in terms of visual spatial memory scores in newly diagnosed T2DM patients.

Pairwise comparison of groups revealed no statistically significant differences at the time of diagnosis in terms of TMT parts A & B (p= 0.333 and p= 0.651). At the end of the follow-up period, we did not determine any statistically significant alteration in terms of processing speed & executive functions in dietary group (p= 0.069 and p= 0.08, respectively) however, we observed a statistically significant improvement in metformin group (p= 0.036 and p= 0.001, respectively). In a study that did not specify the duration of the diagnosis of diabetes, it was observed that TMT-B scores were statistically higher in metformin group compared to other forms of diabetes treatment (9). Our results support the positive effect of metformin on executive functions, similar to the results of Herath et al (9).

Our prospective study has some limitations. Although patients diagnosed with depression were not included in the study, Beck depression test was not used to distinguish the patients with depression who have not been diagnosed yet. Besides, Metformin doses and HbA1c levels have not been evaluated. We designed our study with a minimum sample size of twenty-six per each study group, which may be considered relatively small, even though the power of our study was found to be 91%. An experimental study with a larger number of samples may change the cognitive test results. In this study, we aimed to evaluate the effects of metformin or dietary treatments on cognitive functions only in newly diagnosed T2DM patients at the end of a six-month follow-up period. We believe that different results could be obtained with other diabetes treatment modalities at the end of a longer follow-up period.

To the best of our knowledge, in the current literature, there are no studies investigating the short-term effects of metformin or dietary treatment on verbal memory, visual spatial memory, simple attention & working memory and processing speed & executive functions in newly diagnosed diabetes patients.

In conclusion, we determined a statistically significant improvement in verbal memory scores, which were affected at the time of diagnosis, with metformin and dietary treatment at the end of six-month of follow-up period. Besides, at the end of the follow-up, metformin treatment resulted a statistically significant improvement in terms of visual spatial memory and processing speed & executive function scores. We recommend further evidence-based, prospective studies with a larger number of patients, which observed for the longer time.

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**Ethical Approval**

Approval for this prospective study was granted by Institutional Review Board of Baskent University (Approval Code: KA10/81).

**Conflicts of Interest**

The authors declare that they have no conflict of interest.

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**Author Contrubitons**

**Ceyda Tanoğlu:** Conceptualization, Writing, Review & Editing, Investigation, **Yıldız Kaya:** Writing, Review & Editing, Methodology, **Ülkü Sibel Benli:** Methodology, Conceptualization, Supervision, **Neslihan Başçıl Tütüncü:** Investigation, Methodology

**Review Process**

Extremely reviewed and accepted.

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