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Impact of Sodium-glucose Cotransporter 2 Inhibitors on Cognitive Function in Turkish Older Adults with Type 2 Diabetes: A Controlled 26-Week Study

Sodyum-Glukoz Kotransporter 2 İnhibitörlerinin Tip 2 Diyabetli Türk Yaşlı Bireylerde Bilişsel Fonksiyon Üzerine Etkisi: Kontrollü 26 Haftalık Çalışma

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ABSTRACT

Objective: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are primarily used for renal and cardiovascular protection in type 2 diabetes mellitus (T2DM). It was aimed to survey the effects of SGLT-2 inhibitors on cognitive function in Turkish older adults at 26 weeks follow-up.

Materials and Methods: This prospective, controlled study included 153 participants aged ≥60, comprising 72 type 2 diabetic patients initiating SGLT-2 inhibitors and 81 non-diabetic controls. Comprehensive geriatric assessments, laboratory evaluations, and cognitive and functional tests were conducted at baseline and after 26 weeks. Group comparisons and within-group changes were analyzed using appropriate statistical methods, including repeated measures ANOVA and ANCOVA.

Results: Among the 153 participants, the mean age and frequency of female gender were similar between groups ($p>0.05$), though body mass index (BMI) and comorbidity burden were higher in the SGLT-2 inhibitor group ($p<0.05$). Cognitive performance, particularly total standardized mini-mental state examination (SMMSE) scores, was significantly different in the SGLT2 inhibitor group at baseline ($p<0.05$). After 26 weeks, significant improvements in metabolic parameters were observed in the SGLT2 inhibitor group, but the record subdomain of SMMSE declined ($p<0.05$). This decline lost significance after adjusting for changes in BMI, HbA1c, and 25-hydroxy vitamin D ($p>0.05$). Subgroup analysis revealed cognitive benefit in those using dipeptidyl peptidase-4 (DPP-4) inhibitors alongside SGLT2 inhibitors ($p<0.05$).

Conclusion: SGLT-2 inhibitors appear to be cognitively safe in older Turkish adults within geriatric clinical practice. Although a decline in registration performance was observed at the 26-week follow-up, this effect was not evident when glycemic control, optimal weight management, and adequate vitamin D supplementation were maintained.

Keywords: Cognition, Diabetes Mellitus, Sodium-Glucose Cotransporter 2 Inhibitor, Aging

ÖZ

Amaç: Sodyum-glukoz kotransporter 2 (SGLT-2) inhibitörleri, tip 2 diyabetes mellitus (T2DM) tedavisinde esas olarak renal ve kardiyovasküler koruma amacıyla kullanılmaktadır. Bu çalışmada, SGLT-2 inhibitörlerinin Türk yaşlı bireylerde bilişsel fonksiyon üzerine etkilerinin 26 haftalık takip süresince değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Prospektif ve kontrollü olarak tasarlanan bu çalışmaya, yaşları ≥60 olan toplam 153 birey dahil edildi. Katılımcıların 72'si SGLT-2 inhibitörü tedavisine yeni başlayan T2DM hastalarından, 81'i ise diyabeti olmayan kontrol grubundan

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oluştu. Tüm katılımcılara başlangıçta ve 26. haftada kapsamlı geriatri değerlendirmesi, laboratuvar incelemeleri ile bilişsel ve fonksiyonel testler uygulandı. Gruplar arası ve grup içi değişiklikler uygun istatistiksel yöntemler (tekrarlı ölçümler ANOVA ve ANCOVA) ile analiz edildi.

Bulgular: Toplam 153 katılımcının ortalama yaşı ve kadın cinsiyet oranı gruplar arasında benzerdi ($p>0.05$). Ancak, SGLT-2 inhibitörü kullanan grupta vücut kitle indeksi (VKİ) ve komorbidite yükü daha yüksek bulundu ($p<0.05$). Başlangıçta bilişsel performans, özellikle standardize mini mental durum muayenesi (SMMSE) toplam skorları açısından SGLT-2 grubunda farklılık gösterdi ($p<0.05$). Yirmi altı haftalık takip sonunda, SGLT-2 grubunda metabolik parametrelerde anlamlı düzelmeler gözlendi. Bununla birlikte, SMMSE'nin kayıt (registration) alt boyutunda düşüş saptandı ($p<0.05$). Bu düşüş, VKİ, HbA1c ve 25-hidroksi vitamin D değişimleri için düzeltme yapıldığında anlamlılığını kaybetti ($p>0.05$). Alt grup analizinde, SGLT-2 inhibitörlerini dipeptidil peptidaz-4 (DPP-4) inhibitörleri ile birlikte kullananlarda bilişsel olumlu olarak gözlendi ($p<0.05$).

Sonuç: SGLT-2 inhibitörleri, geriatri pratiğinde Türk yaşlı bireylerde bilişsel açıdan güvenli görünmektedir. Her ne kadar 26 haftalık takipte kayıt alt boyutunda bir gerileme izlense de, glisemik kontrolün sağlanması, uygun kilo yönetimi ve yeterli vitamin D desteği ile bu etkinin ortadan kalktığı görülmüştür.

Anahtar Kelimeler: Bilişsel Fonksiyon, Diyabetes Mellitus, Sodyum-Glukoz Kotransporter 2 Inhibitörü, Yaşlanma

INTRODUCTION

The world is experiencing a rapid demographic transformation, and the proportion of older adults is increasing globally. This shift is accompanied by a rise in age-related conditions. In parallel, the burden of comorbidities also rises, particularly chronic diseases such as hypertension and diabetes mellitus (DM) (1). It is also well known that the burden of comorbidities can be associated with geriatric syndromes that increase in frequency with age, such as dementia, polypharmacy, and frailty in older adults (2). Type 2 diabetes mellitus (T2DM) is the most common form of diabetes in older adults, and its prevalence increases with age until around the age of 70 (3). Chronic complications of diabetes are also more frequently observed in the elder population (4).These include microvascular complications including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as coronary artery disease, peripheral artery disease, and stroke (4). In older adults, the chronic complications of T2DM are related to reduced quality of life, disability, and a heightened risk of mortality (5). T2DM is a major risk factor for dementia, Parkinson's disease and other neurodegenerative disorders (6) Mechanisms explaining the relationship between T2DM and dementia include impaired intracellular insulin signaling pathway, mitochondrial dysfunction, oxidative stress, and inflammatory responses (6). Cognitive assessment is an essential component of geriatric care, as dementia remains a major contributor to reduced life expectancy and increased mortality in the older people (7). Notably, neurocognitive dysfunction is more common in older people with T2DM compared to their non-diabetic counterparts (5).

The management of T2DM has recently undergone significant advancements. Novel anti-diabetic agents such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are increasingly incorporated into treatment regimens. Among these, SGLT-2 inhibitors offer not only glycemic control but also substantial cardiovascular and renal protective benefits, including a reduction in cardiovascular mortality (8). Their antihypertensive properties have also been highlighted in recent studies (9). SGLT-2 inhibitors are considered safe and well-tolerated in individuals aged 65 to 84 years, with cardio-renal benefits persisting with age (10). However, close monitoring is advised for patients aged ≥85 years, as well as those with reduced estimated glomerular filtration rate (eGFR) or increased frailty (11). The neuroprotective effects of SGLT-2 inhibitors remain a topic of debate. An observational study reported that both SGLT-2 inhibitors

and GLP-1 receptor agonists were related to a reduced risk of Alzheimer's disease (12). In contrast, a meta-analysis found no significant reduction in the risk of all-cause dementia with cardioprotective glucose-lowering agents, including SGLT-2 inhibitors (13). Consequently, current evidence regarding the impact of SGLT-2 inhibitors on neurocognitive performance is limited. To date, no studies have specifically investigated their effects on standardized cognitive assessments or explored which cognitive subdomains may be primarily affected.

The aim of this study was to investigate the metabolic effects of SGLT-2 inhibitors, with a particular focus on comprehensive geriatric assessment (CGA) parameters, including cognitive function, over a 26-week follow-up period in older Turkish people. Additionally, analysis of cognitive subdomains offers secondary insight into domain-specific cognitive patterns during SGLT-2 inhibitor therapy within a CGA framework.

MATERIALS AND METHODS

Study Design

In the present study, 247 SGLT2 inhibitor-naive older adults who presented to our outpatient geriatric clinic between January 2023 and January 2024 were initially evaluated. After excluding participants with incomplete medical records and those who did not meet the inclusion criteria during the baseline and follow-up periods, a total of 153 participants were finally assessed. Figure 1 presents the participant flow chart. The participants were divided into two groups: 72 patients with T2DM who were scheduled to initiate SGLT2 inhibitor therapy, and 81 non-diabetic individuals who served as the control group. Both groups were re-evaluated after 26 weeks. No oral antidiabetic medication or insulin treatment was initiated or discontinued during the follow-up period.

Inclusion Criteria

Patients over the age of 60 who had been diagnosed with T2DM, had undergone a Comprehensive Geriatric Assessment, and had no prior history of SGLT2 inhibitor use were included in the study, along with a non-diabetic control group.

Exclusion Criteria

Exclusion criteria included individuals under 60 years of age; those diagnosed with type 1 DM; patients with dementia, alcohol or substance use disorders, acute liver or kidney disease; those deemed unsuitable for SGLT2 inhibitor therapy (e.g., due to recurrent urinary tract infections); individuals with serious conditions such as acute cardiovascular or cerebrovascular events, sepsis, or gastrointestinal bleeding; prior use of SGLT2 inhibitors; discontinuation of SGLT2 inhibitors or changes in antidiabetic treatment during the 6-month follow-up period; hypertriglyceridemia (>600 mg/dL); a history of malignancy; and an estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) formula, of less than 30 mL/min/1.73 m^2.

Patients' Characteristics

Demographic characteristics-including age, sex, educational status, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared)-were obtained for all participants. The presence of hypertension; peripheral artery disease; chronic cerebrovascular, cardiovascular, and pulmonary diseases; and the Charlson Comorbidity Index (CCI) were also assessed. Geriatric syndromes, including urinary incontinence, recurrent falls within the past year, and geriatric depression, were evaluated. In addition, the number of medications used by each participant was documented.

Laboratory Findings

Measurements of metabolic parameters were performed after at least 8 hours of fasting. Hemoglobin, creatinine, sodium, fasting plasma glucose (FPG), HbA1c, alanine aminotransferase, lipid profile, thyroid stimulating hormone, B12 and 25-hydroxy vitamin D levels were performed as laboratory findings. All biochemical tests were analyzed by Diagnostic Modular Systems auto-analyzer (Roche E170 and P-800). Serum 25-hydroxy vitamin D level was measured by radioimmunoassay method.

Comprehensive Geriatric Assessment

For neurocognitive assessment, Standardized Mini Mental State Examination (SMMSE) and its subdomains (time orientation, space orientation, recording, attention, recall, language, visuospatial), Yesevage Geriatric Depression

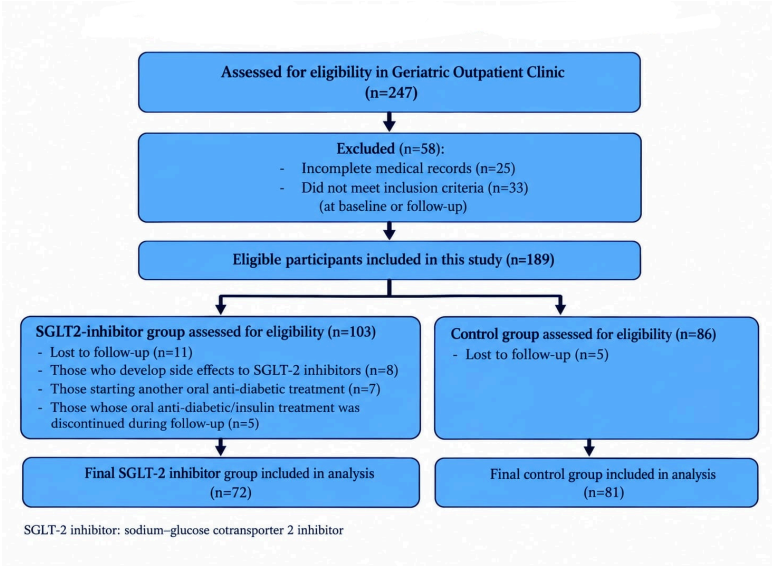

Figure I. Flowchart of the present study

Scale (YGDS) for mood assessment, Lawton-Brody Instrumental Activities of Daily Living Scale (ADLs) and Basic ADLs (Barthel Index) , timed up and go test along with Tinetti Performance and Mobility Assessment (POMA) for the evaluation of gait and balance, and Mini Nutritional Assessment- Short Form (MNA-SF) for nutritional status assessment were performed (14-18).

Diagnosis T2DM

The diagnosis of T2DM was confirmed by one of the following criteria: FPG value, 75 g oral glucose tolerance test (OGTT) second hour plasma glucose value, or HbA1c according to the American Diabetes Association Classification and Diagnosis of Diabetes: Diabetes Care Standards-2025 criteria (5).

26-week Follow-up

We selected 26 weeks because it aligns with commonly used 24-26 week efficacy windows in glucose-lowering drug trials (e.g., HbA1c change is frequently assessed at ~24 weeks in regulatory/clinical trial frameworks), and because a prior geriatric diabetes study evaluating cognitive outcomes also used a 26-week follow-up, supporting the feasibility of detecting short-term cognitive domain changes over a similar timeframe (19,20). BMI, SMMSE and its subdomain, YGDS, POMA score, timed up and go test duration, basic and instrumental ADLs, MNA-SF scores and laboratory values were examined after the 26-week follow-up and compared with baseline values between the patient and control groups. Within the scope of subgroup analyses, patients using SGLT-2 inhibitors were also evaluated according to their concurrent metformin, DPP-4 inhibitor and insulin use. In these subgroups, changes in BMI, HbA1c, SMMSE total score and its domains after 26 weeks were shown with delta (Δ) signs and they were also compared.

Sample Size

In a 2014 study, assuming a diabetes prevalence of 8% among geriatric patients, a minimum sample size of 110 was determined to achieve a 95% confidence level with a 3% margin of error (21).

Statistical Analysis

In this study, categorical variables were presented as percentages (%), and continuous variables were expressed as mean±standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of distribution. For baseline comparisons between the control and patient groups, the Chi-square test was employed for categorical variables. Continuous variables were analyzed using either parametric or non-parametric tests based on the normality of distribution; specifically, the Student's t-test was used for normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables.

The Wilcoxon signed-rank test was applied to compare baseline and 26-week follow-up measurements within each group. Changes in MMSE registration domain scores over the 26-week period were analyzed using repeated measures ANOVA to evaluate within-subject effects. Additionally, repeated measures ANCOVA was conducted to adjust for potential confounding factors, including changes in body mass index (ΔBMI), hemoglobin A1c (ΔHbA1c), and 25-hydroxyvitamin D levels (ΔVit D). A p-value of<0.05 was considered statistically significant in all analyses. Statistical analyses were performed using IBM SPSS Statistics software (Version 22.0; IBM Corp., Armonk, NY, USA)

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the relevant Balıkesir University Ethics Committee (decision no: 2024/20, date: 21 February 2024). All procedures involving human participants were reviewed and approved prior to study initiation.

RESULTS

Among the 153 participants, the mean age was 69.9±4.55 years, and 62.7% were female. When baseline characteristics were compared between the group initiating SGLT2 inhibitor therapy (SGLT2-I group) and the control group, age and sex were similar between these groups (p>0.05). The BMI was significantly lower in the SGLT2-I group. Additionally, the frequency of hypertension and coronary artery disease, as well as CCI scores, were greater in the SGLT2-I group compared to the control group. There were no statistically significant differences between groups in terms of geriatric syndromes. However, FPG, thyroid-stimulating hormone (TSH), vitamin B12, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were significantly lower in the control group, while serum the level of sodium was lower in the SGLT2-I group (p<0.05; Table I).

Table I. Baseline comparison of demographic characteristics. Comorbidities, geriatric syndromes, and laboratory findings between SGLT-2 inhibitor users and control group

	Control group n:81	**SGLT2-I group n:72**	**p-value**
Demographic features (%)			
Age (mean±sd)	73±4.3	69.4±4.8	0.111
Sex(female) (%)	67.9	56.9	0.162
Education year (mean±SD)	6.6±3.2	5.8±2.8	0.089
BMI (kg/m^2) (mean±SD)	27.1±2.1	25.9±2.1	0.029
Comorbidities (%)			
Hypertension	59.3	81.9	0.002
Peripheral arterial disease	4.9	1.4	0.218
Congestive heart failure (stage<2)	4.9	8.3	0.396
Coronary artery disease	16.0	34.7	0.008
Chronic obstructive pulmonary disease	6.3	2.8	0.308
Charlson Comorbidity Index	0.5±1.2	1.8±1	<0.001
Geriatric syndromes			
Urinary incontinence (%)	33.3	34.7	0.856
Geriatric depression (%)	32.5	16.7	0.240
Recurrent falls (≥2 in the past year) (%)	21.0	11.1	0.099
Number of medications (mean±SD)	6±2.6	5.2±2.1	0.298
Laboratory findings (mean±SD)			
Hemoglobin (g/dL)	13.5±1.7	12.9±1.6	0.305
eGFR (mL/min)	76.6±14.3	73.7±18.7	0.535

Table I *(Continued).* Baseline comparison of demographic characteristics. Comorbidities, geriatric syndromes, and laboratory findings between SGLT-2 inhibitor users and control group

	Control group n:81	SGLT2-I group n:72	p-value
Sodium (mmol/L)	140±2.3	137±2.7	<0.001
Fasting plasma glucose (mg/dL)	95±9.4	167±67.3	<0.001
ALT (IU/L)	18±5.6	19±8.8	0.613
HDL (mg/dL)	45±11.6	51±12.2	<0.001
LDL (mg/dL)	134±39	124±44	0.178
Triglyceride (mg/dL)	156±70.8	176±107	0.003
25-OH D vitamin (µg/L)	19.5±12.5	19.7±11.2	0.380
Vitamin B12 (ng/L)	557±163.7	319±291.8	<0.001
TSH (mIU/L)	1.3±0.8	2±1.4	0.005

ALT: Alanine aminotransferase, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, HDL: High density lipoprotein, LDL: Low density lipoprotein, SGLT-2: Sodium-glucose co-transporter 2, TSH: Thyroid stimulating hormone, SD: Standard deviation

At baseline, when CGA parameters-including the Standardized Mini-Mental State Examination (SMMSE) and its subdomains-were compared between these groups, the total SMMSE score was statistically significant in the SGLT2-I group (23.6±3.9) compared to the control group (28.1±1.6; p<0.001). Furthermore, all subdomains except the record domain were different between the groups. Among other CGA measures, the SGLT2-I group had significantly higher scores on the YGDS, POMA, and MNA-SF, whereas the control group had higher scores in BADLs (p<0.05; Table II).

Table II. Comparison of SMMSE global score and its subdomains, other CGA parameters between groups using and not using SGLT-2 inhibitors

	Control group	SGLT2-I group	p-value
SMMSE	28.1±1.6	23.6±3.9	<0.001
Temporal orientation	4.8±0.3	3.9±1	<0.001
Spatial orientation	4.9±0.2	4.0±0.9	<0.001
Record	2.9±0.1	2.9±0.2	0.310
Attention	3.9±0.8	2.8±1.5	<0.001
Recall	2.7±0.4	1.9±0.9	<0.001
Language	7.9±0.2	7.5±0.7	<0.001
Visuospatial	0.7±0.4	0.3±0.4	<0.001
YGDS	2.7±3.4	3.3±2.8	0.047
POMA	25.8±2.5	26.7±1.9	0.017
Timed up and go test duration (sec)	11.4±2.7	11.7±2.5	0.409
BADLs	97.4±3	94.2±6.7	0.004
IADLs	20.9±2.3	20.2±3.2	0.489
MNA-SF	12.1±2.2	13.0±1.4	0.028

BADL: Basic activities of daily living, CGA: Comprehensive geriatric assessment, IADL: Instrumental activities of daily living, MNA-SF: Mini nutritional assessment-short form, POMA: Performance-oriented mobility assessment, SMMSE: Standardized mini-mental state examination, YGDS: Yesavage geriatric depression scale

During the 26-week follow-up period, the SGLT-2 inhibitor group exhibited significant reductions in BMI, hemoglobin A1c (HbA1c), low-density lipoprotein (LDL) cholesterol levels, and the urine albumin-to-creatinine ratio. In contrast, levels of 25-hydroxyvitamin D and HDL cholesterol significantly increased ($p<0.05$). While no significant change was observed in the global SMMSE score over time ($p>0.05$), a statistically significant decline was noted specifically in the registration subdomain ($p=0.008$; Table III).

Table III. Comparison of baseline and 24-week follow-up values between SGLT-2 inhibitor users and non-users

	Control group			**SGLT2-I group**		
	Baseline	**24-week follow-up**	**p value**	**Baseline**	**24-week follow-up**	**p value**
BMI (kg/m^2)	**27.1±2.1**	**26.6±2.3**	**0.571**	**25.9±2.1**	**25.3±2.2**	**<0.001**
SMMSE	28.1±1.6	28±1.9	0.555	23.6±3.9	23.9±3.8	0.158
Temporal orientation	4.8±0.3	4.8±0.3	0.796	3.9±1	4.0±0.8	0.319
Spatial orientation	4.9±0.2	4.8±0.3	0.782	4.0±0.9	4.1±0.9	0.635
Record	2.9±0.1	2.9±0.1	0.564	2.9±0.2	2.8±0.4	0.008
Attention	3.9±0.8	4.0±0.9	0.543	2.8±1.5	3.1±1.5	0.111
Recall	2.7±0.4	2.6±0.5	0.819	1.9±0.9	2.0±0.9	0.247
Language	7.9±0.2	7.9±0.1	0.317	7.5±0.7	7.4±1	0.819
Visuospatial	0.7±0.4	0.7±0.4	0.197	0.3±0.4	0.3±0.4	1.0
YGDS	2.7±3.4	2.1±3.2	0.006	3.3±2.8	3.1±2.2	0.649
POMA	25.8±2.5	26.2±2.4	0.037	26.7±1.9	26.8±1.9	0.403
TUG duration (sec)	11.4±2.7	10.7±2.8	0.028	11.7±2.5	11.7±2.2	0.644
BADLs	97.4±3	97±3.8	0.172	94.2±6.7	94.3±6.1	0.717
IADLs	20.9±3	19.7±3.7	<0.001	20.2±3.2	20.3±3.1	0.351
MNA-SF	12.1±2.2	12.8±1.8	0.006	15.1±3.1	14.9±3	0.391
Hemoglobin (g/dL)	13.5±1.7	13.2±1.3	0.788	12.9±1.6	13±1.4	0.606
eGFR (mL/min)	76±14.3	76±21.3	0.735	73.7±18.7	72±19	0.055
Sodium (mmol/L)	140±2.3	139±1.8	0.645	137.0±2.7	137±2.3	0.563
Fasting glucose (mg/dL)	95±9.4	92±8.1	0.326	167±67.3	147±52.5	0.300
HBa1c (%)				8.4±1.8	7.6±1.2	<0.001
ALT (IU/L)	18±5.6	17.4±6.2	0.016	19±8.8	19.9±10.5	0.542
HDL-C (mg/dL)	45±11.6	59.6±11.5	0.480	51±12.2	53.6±10.9	0.014
LDL-C (mg/dL)	134±39	137.2±38.6	0.861	124±44.1	108.6±41.7	<0.001
25-OHD (µg/L)	19.5±12.5	28.6±13.2	<0.001	19.7±11.2	27.2±12.2	<0.001
Vitamin B12 (ng/L)		515.6±270	0.830	319.7±291.8	312.4±190	0.565
TSH (mIU/L)	1.3±0.8	1.4±1.2	0.814	2±1.4	2.1±1.4	0.328
Albumin/Creatinine Ratio (mg/g)				320±1003.1	213.8±340.1	0.011

25-OHD: 25-hydroxy-vitamin D, ALT: Alanin aminotransferase, BADLs: Basic activities of daily living, BMI: Body mass index, CGA: Comprehensive geriatric assessment, eGFR: Estimated glomerular filtration rate, HDL-C: High density lipoprotein- cholesterol, IADLs: Instrumental activities of daily living, LDL-C: Low density lipoprotein- cholesterol, MNA-SF: Mini nutritional assessment-short form, POMA: Performance-oriented mobility assessment, SMMSE: Standardized mini-mental state examination, TUG: Timed up and go test, TSH: Thyroid stimulating hormone, YGDS: Yesavage geriatric depression scale

In the sub-analysis of participants receiving SGLT-2 inhibitors, a statistically significant improvement in total SMMSE score was observed in those who were concurrently using a Dipeptidyl Peptidase-4 (DPP-4) inhibitor compared to those who were not (ΔSMMSE: -0.32±1.54 vs. 0.61±1.27; p=0.008). In contrast, changes in SMMSE scores were not statistically significant in participants using metformin or insulin compared to those not using these agents (p>0.05; Table IV).

Table IV. Comparison of the effects of concurrent metformin, DPP-4 inhibitor and/or insulin use on changes in SMMSE and record subdomain, BMI and Hba1c values in the SGLT-2 inhibitor group at 24-week follow-up

	Metformin group			**DPP4-inhibitor group**			**Insulin group**		
	(+) n=51	**(-) n= 21**	**p value**	**(+) n=28**	**(-) n= 44**	**p value**	**(+) n=26**	**(-) n= 46**	**P value**
ΔBMI	-0.51±1.15	-0.54±0.97	0.833	-0.81±1.53	-0.34±0.65	0.360	-0.41±0.92	-0.58±1.19	0.573
ΔSMMSE	0.19±1.51	0.38±1.32	0.676	-0.32±1.54	0.61±1.27	0.008	-0.07±1.44	0.48±1.43	0.149
ΔHbA1c	-1.04±1.48	-1.16±1.62	0.281	-0.96±1.80	-0.66±1.33	0.885	-0.85±1.42	-0.74±1.60	0.935
ΔSMMSE- Record	-0.09±0.36	-0.23±0.53	0.177	-0.21±0.41	-0.09±0.42	0.240	-0.15±0.36	-0.13±0.45	0.865

BMI: Body mass index, DDP4-I: Dipeptidyl Peptidase-4 Inhibitor, SMMSE: Standardised mini-mental state examination

In the unadjusted repeated measures ANOVA, the MMSE record domain score demonstrated a statistically significant decline over 24 weeks (mean±SD: 2.94±0.23 at baseline vs. 2.80±0.43 at 24 weeks; F(1,71)=7.819, p=0.007). However, when adjusted for potential confounders-including changes in BMI, HbA1c, and serum 25-hydroxyvitamin D levels-using repeated measures ANCOVA, the difference did not remain statistically significant (p>0.05), indicating that the observed change may be influenced by these covariates. (p>0.05; Table V).

Table V. Changes in MMSE record subdomain score over 24 weeks

Analysis type	**Time point**	**Mean±SD**	**Statistical test**	**p-value**
Unadjusted analysis	Baseline	2.94±0.23	Repeated Measures ANOVA	0.007*
	24 weeks	2.80±0.43	F(1,71)=7.819	
Adjusted analysis (covariates: ΔBMI, ΔHbA1c, ΔVit D)	Baseline & 24 weeks	-	Repeated Measures ANCOVA	0.345 ɬ

*: Statistically significant at p<0.05

ɬ: No statistically significant difference after adjusting for changes in BMI, HbA1c, and 25-OH vitamin D levels

Δ=Change from baseline to week 24

ANCOVA=Analysis of Covariance

DISCUSSION

In this study, no significant change was observed in total cognitive scores in older adults using SGLT-2 inhibitors over the 26-week period. Although a decline was detected in the record subdomain, this difference lost statistical significance after adjustment for changes in body mass index, HbA1c, and serum 25-hydroxyvitamin D levels.

Cognitive assessment is a critical component of geriatric practice. In older adults, cognitive impairment can present along a broad spectrum, ranging from mild forgetfulness to overt dementia. Dementia itself is recognized as a geriatric syndrome and may not always be attributable to neurodegenerative processes alone (22). It is well established that cognitive decline in the older people is also associated

with various geriatric syndromes, including malnutrition, sarcopenia, orthostatic hypotension, and frailty (23-25). Importantly, older adults with T2DM are at increased risk of cognitive dysfunction and institutionalization compared to their non-diabetic peers (5). In this population, factors such as all-cause dementia, Alzheimer's disease, recurrent hypoglycemia, and longer disease duration have been shown to negatively affect cognitive function (5). Recently, the concept of diabetes-related dementia has emerged, referring to a distinct clinical entity characterized by slower progression than typical neurodegenerative dementias, absence of specific neuroimaging findings, and associations with advanced age, elevated HbA1c levels, insulin use, probable sarcopenia, and frailty (5, 26). In our study, even in the absence of a formal dementia diagnosis, cognitive screening scores were lower in the diabetic group compared to the non-diabetic group, in line with findings reported in the literature.

Given the risk of cognitive decline in older adults with DM, it is essential to incorporate cognitive status into treatment planning. In this context, anti-diabetic agents with a high risk of hypoglycemia should be avoided in the older adults. Preference should be given to agents with neutral or potentially beneficial effects on cognitive function. Recently, SGLT-2 inhibitors and glucagon-like peptide-1 receptor agonists have gained prominence in the treatment of T2DM. Both drug classes have been reported to exhibit modest positive effects on cognition (5). A meta-analysis suggested that SGLT-2 inhibitors may offer minimal benefits in slowing cognitive decline (27). However, conflicting evidence exists, with other studies reporting no significant cognitive benefits (28). Furthermore, the specific cognitive domains potentially influenced by SGLT-2 inhibitors have not yet been clearly identified. In our study, SGLT-2 inhibitor use was not associated with any negative impact on global cognitive scores over a 26-week follow-up. A slight decline was observed in the domain of record memory; however, this effect appeared to be mitigated by improvements in HbA1c levels and weight reduction. Indeed, our findings suggest that glycemic control and weight loss achieved through SGLT-2 inhibitor therapy do not exert a cumulative negative effect on overall cognitive function, including memory record.

The effects of SGLT-2 inhibitors on recording memory can be explained by several mechanisms. While SGLT-2 inhibitors have been associated with neuroprotective properties through improvements in glycemic control, reduction in oxidative stress, and enhancement of insulin sensitivity (29), these benefits are generally thought to manifest over longer treatment periods. The 6-month follow-up may not have been sufficient to capture such long-term neurocognitive effects. More specifically, the record domain is sensitive to attention, arousal, and short-term memory, and may be acutely influenced by metabolic or hemodynamic fluctuations (30). One possible explanation is the osmotic diuresis induced by SGLT-2 inhibitors, which can lead to volume depletion and transient cerebral hypoperfusion, particularly in older or frail individuals (31,32). Even mild dehydration may impair attention and working memory performance, potentially contributing to reduced record scores. Additionally, episodes of euglycemic ketoacidosis or rapid shifts in glucose availability due to enhanced urinary glucose excretion might affect neuronal energy supply, particularly in memory-related regions such as the hippocampus (33). Although the decline in record score was initially significant, it lost statistical significance after adjustment for changes in BMI, HbA1c, and serum vitamin D levels. This suggests that the observed cognitive change may be mediated by metabolic alterations rather than a direct effect of SGLT2 inhibition. For instance, reduced vitamin D levels have been independently associated with cognitive impairment, particularly in domains related to attention and memory (34). Moreover, rapid changes in BMI and HbA1c may reflect catabolic stress or increased glycemic variability, both of which have been linked to subtle cognitive dysfunction (35).

Another striking outcome in our study is that when SGLT-2 inhibitor and DPP-4 inhibitor were used together, an improvement was shown in the global SMMSE score. The cognitive effectiveness of DPP4 inhibitors has been studied in the literature. It has been shown that DPP-4 inhibitors have positive effects in terms of cognition and also that there is an improvement in ADLs (36). In addition, positive effects were shown in the area of shape copying after 6 months of follow-up in individuals using vildagliptin, one of the DPP-4 inhibitors (20). The combined use of SGLT-2 and DPP-4 inhibitors may exert synergistic neuroprotective effects, potentially stabilizing MMSE scores through complementary mechanisms. In

parallel, SGLT-2 inhibitors contribute to improved insulin sensitivity, reduced systemic inflammation, and support cerebral metabolism through increased ketone availability and mitochondrial protection (29). However, further large-scale study are needed to confirm these preliminary findings.

Study Limitations

This study has several strengths. First, it employs a longitudinal design and focuses on a specific age group. Second, to our knowledge, it is the first study conducted in Turkish older adults. Third, it explores the effects of SGLT-2 inhibitors on specific cognitive subdomains. Nonetheless, the study has certain limitations. First, a longer follow-up period is needed to assess sustained effects. Second, individuals with diabetes who were not using SGLT-2 inhibitors were not included in the comparative analysis. However, participants who initiated another antidiabetic agent or discontinued their current medication during the follow-up period were excluded from the evaluation. Third, non-pharmacological interventions such as diet and exercise were not taken into account.

CONCLUSION

In conclusion, SGLT-2 inhibitor therapy over 26 weeks was associated with stable global cognitive performance in Turkish older adults, while a transient decline in the registration subdomain was observed but became non-significant after adjustment for changes in body mass index, glycemic control, and vitamin D levels, suggesting that cognitive outcomes are closely linked to metabolic and nutritional status rather than a direct adverse effect of SGLT-2 inhibition.

Conflict of Interests

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the relevant Balıkesir University Ethics Committee (decision no: 2024/20, date: 21 February 2024).

Authors' Contribution

Concept: EP, SEK, Design: EP, SEK, Supervision: EP, SEK, Resources: EP, SEK, Materials: EP, SEK, Data Collection and/or Processing: EP, SEK, Analysis and/or Interpretation: EP, SEK, Literature Search: EP, SEK, Writing Manuscript: EP, SEK

Use of Artificial Intelligence

No artificial intelligence (AI) technologies or AI-assisted tools were utilized in the preparation or production of this study.

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