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ORIGINAL ARTICLE / ÖZGÜN MAKALE

IL-6 LEVELS AND COGNITIVE COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A CROSS SECTIONAL STUDY

TİP 2 DİYABETLİ HASTALARDA IL-6 DÜZEYLERİ VE KOGNİTİF KOMPLİKASYONLAR: KESİTSEL BİR ÇALIŞMA

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ABSTRACT

Objective: *It is important to monitor and manage macrovascular and microvascular complications, which are significant causes of mortality and morbidity in type 2 diabetes (T2DM). Diabetes-related cognitive impairment is an important complication that has recently attracted more attention, but its pathophysiology and clinical features are not known. The aim of this study was to evaluate the potential role of inflammation in diabetes-related cognitive impairment.*
Material and Method: *A total of 122 participants (67 patients with T2DM and 55 controls) took part in this cross-sectional observational clinical study. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA) test. IL-6 levels were measured using the ELISA method on blood samples obtained from the participants.*
Result and Discussion: *Although IL-6 levels increased with diabetes and cognitive impairment, there was no significant difference between the groups ($p>0.05$). Except for attention and orientation, we observed significantly more impaired cognitive performance in T2DM patients. The MoCA total score was significantly correlated with age, education level, fasting glucose, HbA1c, and vitamin D levels ($p<0.05$). Our results found no evidence that IL-6 is involved in the pathophysiology of cognitive impairment in T2DM, but these findings the importance of cognitive screening in monitoring complications associated with diabetes.*
Keywords: *Cognitive impairment, inflammation, type 2 diabetes*

ÖZ

Amaç: *Tip 2 diyabette (T2DM) önemli mortalite ve morbidite nedenleri olan makrovasküler ve mikrovasküler komplikasyonların izlenmesi ve yönetilmesi önemlidir. Diyabetle ilişkili kognitif bozukluk son dönemler daha fazla dikkat çeken önemli bir komplikasyondur, ancak patofizyolojisi ve klinik özellikleri net olarak bilinmemektedir. Bu çalışmanın amacı diyabetle ilişkili kognitif bozuklukta inflamasyonun potansiyel rolünü değerlendirmektir.*
Gereç ve Yöntem: *Bu kesitsel gözlemsel klinik çalışmaya toplam 122 katılımcı (67 T2DM hastası ve 55 kontrol) dahil edilmiştir. Bilişsel performans Montreal Kognitif Değerlendirme (MoCA) testi kullanılarak değerlendirilmiştir. IL-6 düzeyleri katılımcılardan alınan kan örneklerinde ELISA yöntemi kullanılarak ölçülmüştür.*
Sonuç ve Tartışma: *IL-6 düzeyleri diyabet ve bilişsel bozuklukla birlikte artmasına rağmen, gruplar arasında anlamlı bir fark yoktu ($p>0.05$). Dikkat ve oryantasyon dışında, T2DM*

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hastalarında kognitif performansın anlamlı olarak daha fazla bozulduğunu gözlemledik. MoCA toplam skoru yaş, eğitim düzeyi, açlık glukozu, HbA1c ve D vitamini düzeyleri ile anlamlı korelasyon gösterdi ($p<0.05$) Sonuçlarımız IL-6'nın T2DM'de kognitif bozukluğun patofizyolojisinde rol oynadığına dair bir kanıt bulmadı dakat bu bulgular diyabetle ilişkili komplikasyonların izlenmesinde kognitif taramanın önemini vurgulamaktadır.
Anahtar Kelimeler: *İnflamasyon, kognitif bozulma, tip 2 diyabet*

INTRODUCTION

The incidence of Type 2 diabetes mellitus (T2DM) is expected to rise in the coming years due to lifestyle changes, insufficient physical activity, unhealthy diets, and other factors [1, 2]. This disease is particularly common in individuals over 65 and poses significant health challenges for the elderly [3]. An observational study conducted in 28 countries across Asia, Africa, South America, and Europe found that 53.2% of patients with type 2 diabetes mellitus (T2DM) have microvascular complications, and 27.2% have macrovascular complications [4]. As vascular complications are a significant cause of mortality and morbidity in diabetes, effective management of these complications is crucial. Recently, cognitive impairment has emerged as a complication of diabetes that, while attracting growing attention, remains less understood and researched compared to other complications [5].

Patients with T2DM are 1.5 to 2 times more likely to experience cognitive decline, impairment, or dementia compared to non-diabetics.[6]. This is a significant clinical interest, especially given the aging global population and the high prevalence of T2DM among the elderly. Impairments in attention, memory, processing speed, executive function, and general cognitive function have been observed in T2DM patients [7]. Prospective studies indicate that T2DM is a risk factor for dementia and mild cognitive impairment, with the risk of Alzheimer's disease being approximately twice as high in T2DM patients compared to non-diabetics [8,9].

The mechanisms behind cognitive decline in T2DM are not fully understood, but chronic systemic inflammation is thought to play a role [10]. Research into biomarkers to understand brain changes in T2DM patients is growing, with proinflammatory cytokines such as TNF, IL-1, IL-2, and IL-6 being found in excess in the brains of patients with T2DM and Alzheimer's Disease, suggesting inflammation's role in neuronal damage [11]. IL-6, an important inflammatory biomarker, is implicated in the development of insulin resistance and T2DM, where chronic inflammation can initiate pathological processes [12]. Low-grade inflammation in middle age, indicated by IL-6 levels, is linked to cognitive decline in later life [13]. More research is needed to evaluate the potential of inflammatory molecules as predictive and diagnostic biomarkers for diabetes-related cognitive dysfunction [11]. The aim of this study is to investigate the relationship between cognitive impairment and plasma IL-6 levels in patients with T2DM.

MATERIAL AND METHOD

Patients

In this cross-sectional, observational study, 122 patients participated, with 67 diagnosed with T2DM and 55 comprising the control group. Patients presenting to the Internal Medicine Clinic of of Bezmialem Vakif University Hospital were evaluated by an Internal Disease Specialist based on specific inclusion and exclusion criteria. Inclusion criteria required participants to be at least primary school graduates and aged between 30 and 65 years. In our study, the geriatric population over 65 years of age was not included due to the significant increase in the risk of dementia and low-grade inflammation in this age group. Exclusion criteria of both study groups included a neurological or psychiatric diagnosis, insulin therapy, hypothyroidism, vitamin B12 and folic acid deficiency, hypoglycemia-hyperglycemia attacks, and alcohol or drug addiction. All participants signed written informed consent, and approval was obtained from the Bezmialem Vakif University Clinical Research Ethics Committee (05.04.2023/07-2). The study started on 30.04.2023 and concluded on 30.04.2024.

Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) test is a brief cognitive screening tool designed to assist in the detection of mild cognitive impairment. It assesses various cognitive domains, including short-term memory recall, visuospatial abilities, executive functions, attention, working memory, language and orientation. The MoCA test is widely used in clinical settings due to its sensitivity and specificity in identifying mild cognitive impairment and dementia. The test is quick to administer, takes about 10-15 minutes, and provides a total score out of 30 points, with higher scores indicating better cognitive function. A score of 26 or above is considered normal, while lower scores may indicate cognitive impairment [14]. According to a validation study conducted on the Turkish population scores of 21 and above are regarded as normal [15].

Laboratory

Blood samples were collected in the morning following an 8-hour fasting period. They were placed into gel biochemistry tubes and centrifuged at 3500xg for 10 minutes at room temperature. The resulting samples were stored at -80°C until analysis. After obtaining blood samples from the patients and completing their cognitive assessments, the samples were processed collectively. IL-6 levels were measured using the ELISA method with human ELISA kits based on the Sandwich-ELISA principle (Elabscience Cat.No.:E-EL-H6156). All steps of the ELISA experiments were carried out following the protocol provided by the kit manufacturer. The sample protocol can be found at https://www.elabscience.com/p-human_il_6_interleukin_6_elisa_kit-532924.html. Insulin levels, blood sugar levels, and hemogram values related to diabetes were routinely requested from the patients and accessed via the hospital information system.

Statistical Method

All statistical analyses were conducted using IBM SPSS 28.0 software. The Shapiro-Wilk test was used to assess normality. Continuous variables with a normal distribution were reported as mean ± standart deviation (SD), while continuous variables with a non-normal distribution were reported as median (Q1-Q3). For normally distributed variables, comparisons between the diabetes and control groups were made using the t-test, and for non-normally distributed variables, the Mann-Whitney U test was used. The categorical variables were expressed as numbers (percentages) and compared using the chi-square test. A significance level of ≤ 0.05 was considered statistically significant.

RESULT AND DISCUSSION

One hundred and twenty-two patients participated in our study. The mean age of the patients was 49.43 ± 7.10 years, and the mean years of education were 8.66 ± 3.78. Among the participants, 67 were diagnosed with T2DM, while 55 comprised the control group. Demographic and clinical data of the groups were compared in Table 1. Significant differences were observed between the groups in terms of fasting glucose, HbA1c, HOMA-IR, BMI, ALT, LDL, HDL, Mg, neutrophil count, and years of education ($p < 0.05$). Among patients with type 2 DM, 26 (38.8%) exhibited impaired cognition, while cognitive performance was preserved in 41 (61.2%) patients. In contrast, only 5 (9.1%) individuals in the control group had impaired cognition, indicating a significant difference between the two groups.

The cognitive performances of the groups were compared in 2 different models and presented in Table 2. Correction was made for age and education in Model 2. It was determined that cognitive performance in T2DM patients was significantly impaired compared to controls ($p<0.001$). Except for orientation and attention, T2DM patients exhibited poorer performance in all cognitive domains compared to controls.

IL-6 levels were compared between patients with T2DM and controls (Figure1). In the T2DM group, the IL level was 1.27 ± 0.83 while it was 1.18 ± 0.84 in the control group. There was no significant difference between the IL-6 levels of the groups ($p=0.569$). The relationship between IL-6 levels and MoCA total was examined, and no statistically significant difference was found between them ($p>0.05$,$r=0.058$). IL-6 levels were compared between Type 2 DM patients with and without impaired cognition. The IL-6 levels in Type 2 DM patients with impaired cognition were 1.35±0.82, whereas

those with normal cognition were 1.22±0.82. Despite an increase in IL-6 levels in T2DM patients with impaired cognition, there was no significant difference between the two groups (p=0.521). The IL-6 levels of T2DM patients with and without impaired cognition were compared with those of the control group in Figure 1. No significant difference was found among the groups (p=0.691).

The relationship between MoCA total score and other cognitive subdomain scores with clinical and demographic variables was examined. A significant association was found between MoCA total score and age, education, fasting glucose, HbA1c, and vitamin D ($p<0.05$). A significant relationship was observed between visual spatial functions and education, fasting glucose ($p<0.05$). Naming was significantly associated with education, fasting glucose, HbA1c, TSH, and Mg ($p<0.05$). Attention showed a significant relationship with age, education, eGFR, and hemoglobin ($p<0.05$). Language was significantly related to age, education, fasting glucose, B12, and vitamin D ($p<0.05$). Abstract thinking was significantly associated with education and TSH ($p<0.05$). Memory showed significant relationships with education, HbA1c, TSH, and folic acid ($p<0.05$). There was no significant relationship between orientation and clinical and demographic characteristics ($p<0.05$).

Table 1. Demographic and clinical data of the groups

Variables	T2DM (n=67)	Control (n=55)	p
Age(year)	50.48 ± 8.24	48.15 ± 5.21	0.060
Education(year)	5 (5-11)	11 (5-13)	**<0.001**
Gender, male (%)	35 (52%)	20 (36%)	0.080
Cognitive impairment, n (%)	26 (38.8 %)	5 (9,1%)	**<0.001**
BMI(kg/m²)	30.65±4.76	27.41± 3.92	**<0.001**
Fasting Glucose(mg/dl)	143 (122-177)	92 (89-95)	**<0.001**
HbA1c(%)	7.28 (6.45-8.10)	5.24 (5.11-5.49)	**<0.001**
Iron(µg/dl)	79.12 ± 36.06	91.67 ± 41.13	0.210
AST(U/L)	18.81 ± 5.44	18.89 ± 5.01	0.954
ALT(U/L)	27.49 ± 15.25	22.13 ± 10.50	**0.050**
HOMA-IR	2.83 ± 1.28	1.83 ± 0.84	**0.003**
LDL(mg/dl)	137.81 ± 46.29	124.13 ± 26.66	**0.050**
HDL(mg/dl)	48.44 ± 11.60	54.79 ± 14.07	**0.037**
TSH(mU/L)	2.68 ± 5.87	1.82 ± 1.00	0.326
Triglyceride (mg/dl)	157.15 ± 77.30	130.21 ± 71.39	0.073
B12(ng/l)	333.82 ± 147.60	337.28 ± 86.30	0.877
Folic Acid(µg/l)	8.01 ± 2.92	10.54 ± 14.78	0.279
Vitamin D(µg/l)	20.33 ± 10.91	23.86 ± 13.22	0.270
Ca(mg/dl)	9.55 ± 0.40	9.52 ± 0.42	0.814
Na(mmol/l)	139 (138-141)	140 (139-140)	0.210
K(mmol/l)	4.51 ± 0.56	4.33 ± 0.24	0.095
Mg(mg/dl)	1.87 ± 0.21	1.97 ± 0.15	**0.042**
Urea(mg/Dl)	29.96 ± 8.34	26.44 ± 7.03	0.092
eGFR(ml/min/1.73 m²)	94.37 ± 13.61	96.44 ± 12.09	0.472
Creatinine(mg/dl)	0.82 ± 0.14	0.77 ± 0.15	0.104
Neutrophil(10^3/ul)	4.41 ± 1.35	3.79 ± 1.20	**0.015**
Lymphocyte (10^3/ul)	2.70 ± 0.70	2.29 ± 0.55	**0.001**
Hemoglobin(g/l)	14.19 ± 1.62	13.73 ± 1.93	0.198
Platelet(10^3/ul)	259.29 ± 55.48	258.22 ± 83.67	0.937

For normally distributed variables, mean ± SD values are presented, while for non normally distributed variables, median (Q1-Q3) values are provided. The statistically significant ones are bolded T2DM,.type 2 diabetes; BMI, body mass index; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDL, Low-Density Lipoprotein; HDL,High-Density Lipoprotein, TSH, Thyroid-stimulating hormone; eGFR, Estimate Glomerular Filtration Rate

Table 2. Comparison of cognitive performances between groups

Cognitive domain	Model 1			Model 2		
	T2DM (n=67)	Control (n=55)	p	T2DM (n=67)	Control (n=55)	p
MoCA Total score	21.52±4.39	25.22±2.942	**<0.001**	22.10±3.36	24.44±3.41	**<0.001**
Visuospatial/Executive	3.58±1.11	4.29±0.99	**<0.001**	3.68±1.02	4.14±1.03	**0.017**
Naming	3 (2-3)	3 (3-3)	**<0.001**	2.49±0.51	2.80±0.52	**0.002**
Attention	5 (4-6)	6 (5-6)	0.065	4.82±1.26	4.90±1.29	0.741
Language	1 (0-2)	2 (1-3)	**<0.001**	1.44±0.94	1.88±0.96	**0.015**
Abstraction	1.28±0.75	1.65±0.55	**0.003**	1.33±0.67	1.58±0.68	**0.047**
Memory	2.46±1.39	3.31±1.35	**<0.001**	2.51±1.41	3.22±1.43	**0.009**
Orientation	6 (6-6)	6 (6-6)	0.227	5.83±3.76	5.88±0.38	0.451

Normally distributed continuous variables were presented as mean ±SD, non-normally distributed continuous variables were presented as median (Q1-Q3). Model 1 represents the T2DM and control groups, whereas correction has been made for age and education in Model 2. The statistically significant ones are bolded. T2DM,.type 2 diabetes; MoCA, The Montreal Cognitive Assessment

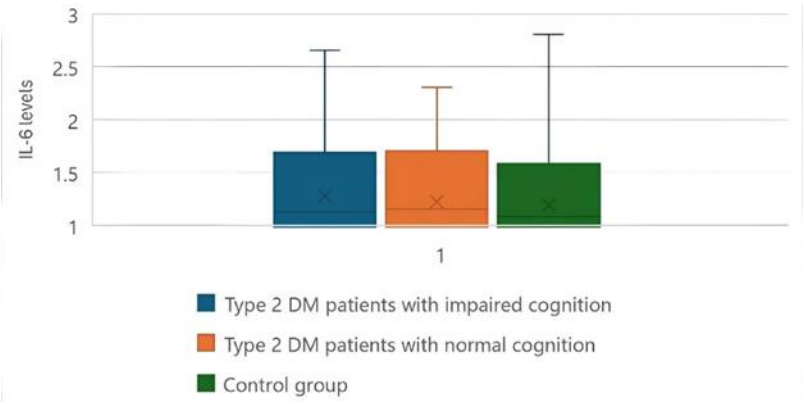

Figure 1. Comparison of IL-6 levels among groups
No significant difference was found between the groups (p=0.691)

This study aimed to investigate the relationship between cognitive impairment and IL-6 levels in middle-aged T2DM patients and to contribute to the literature on the potential role of inflammation in diabetes-related cognitive impairment. IL-6 levels of the groups were compared and no significant difference was found (p<0,05). Our study demonstrated that, except for attention and orientation, T2DM patients exhibited notably lower scores across other cognitive subdomains. We observed a marked cognitive impairment in T2DM patients compared to controls. We further explored the correlation between the Montreal Cognitive Assessment (MoCA) total score, cognitive subdomain scores, and various clinical and demographic variables. A significant association emerged between MoCA total score and age, education level, fasting glucose, HbA1c, and vitamin D levels (p<0.05).

The transition of T2DM from a metabolic phenomenon to one mediated by inflammation has been noted in previous studies [16]. The activation of the inflammation cascade and endothelial dysfunction are significant in both the development of diabetes and the pathophysiological mechanisms underlying diabetes-related complications [17]. The irregular elevation of inflammatory markers is believed to influence glycemic control and insulin sensitivity, contributing to the pathogenesis of T2DM. Although IL-6 typically exists at appropriate levels, its dysregulated production and prolonged exposure can lead to inflammation [18]. However, the role of IL-6 as an early biomarker for T2DM remains uncertain. IL-6 is a versatile inflammatory cytokine known for its multifaceted biological effects. In this study, we observed that IL-6 levels were increased in patients with type 2 diabetes but did not show a significant difference compared to controls. Various pathways have been proposed to explain the relationship between diabetes and cognitive complications. These include vascular system damage, protein

misfolding, and inflammation or oxidation, which can promote both neurodegenerative and vascular damage [19]. The presence of low-grade inflammation in middle-aged individuals has emerged as an independent risk factor for compromised cognitive function in later stages of life, with IL-6 being proposed as a potent biomarker for cognitive performance and decline [13]. Chronic inflammation and endothelial dysfunction caused by elevated IL-6 levels can affect cerebral blood flow and promote neurodegenerative processes, leading to cognitive decline. Inflammation has been highlighted as a key pathway that can impair cerebral vasoregulation, potentially leading to cognitive decline in individuals with diabetes [20]. Data from longitudinal studies indicate that elevated IL-6 levels may increase the risk of cognitive decline and dementia [21]. While some studies in the literature reported a relationship between IL-6 levels and cognitive functions [22, 23], others did not observe a significant relationship [24-26]. In our study, unlike some results, we did not find a statistically significant difference between IL-6 levels and MoCA total score and cognitive subdomain scores. In the Edinburgh Type 2 Diabetes Study, levels of three pro-inflammatory markers (IL-6, TNF-α, and CRP) were associated with poorer cognitive performance in 1,066 elderly adults with T2DM, most of whom had complications associated with T2DM identified [27]. Evidence is increasing in the general population suggesting that inflammatory markers can predict cognitive change. A prospective cohort study found that higher baseline levels of fibrinogen and IL-6 were associated with greater cognitive decline over a 10-year follow-up [27]. Cognitive impairment in diabetes is thought to be determined by multiple etiologies, some of which are specific to diabetes, and may be related to complex pathologies that vary between individuals [28]. When we consider our results alongside existing literature, it appears that research on the impact of IL-6 on cognitive impairment in diabetes is limited, and the findings appear to be inconsistent. Therefore, it is likely that in such a complex pathology, observing the impact of inflammation through a single biomarker, as in our study, can be challenging.

Given the burgeoning aging population worldwide and the heightened prevalence of T2DM among the elderly, understanding the disease's adverse effects on health and cognitive function holds significant clinical importance. Awareness of diabetes' other complications is better established compared to cognitive impairment [29]. Future studies aim to clearly elucidate the role of inflammation in cognitive impairment in diabetes, potentially investigating the role of anti-inflammatory treatments or newly developed drugs in preventing these complications. The smaller size of our study group compared to other large-scale studies is a limitation that restricts and undermines the reliability of the outcome. More research should be conducted in middle age to prevent the complications of T2DM and consider preventive treatment options. Also antihyperglycemic treatments have been found to change biomarkers linked to inflammation [30-32]. So, our study is limited by the lack of standardization of antihyperglycemic therapy in T2DM patients. Future research will explore the impact of antihyperglycemic therapy and other medications on these biomarkers, providing a more comprehensive understanding of their relationship.

In conclusion, we observed a significant cognitive impairment in patients with T2DM. This underscores the importance of cognitive screening in monitoring complications associated with diabetes. We observed that both diabetes and cognitive impairment increased IL-6 levels, but the increase was not significant. Our results found no evidence that IL-6 is involved in the pathophysiology of cognitive impairment in T2DM. Future studies with larger samples may capture significant evidence of the elevated levels of IL-6 that we observed. Identifying the cognitive complications and biomarkers of T2DM is crucial. Future studies in this area could provide a broader understanding of the pathology, leading to early detection and significant progress in the treatment of complications.

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AUTHOR CONTRIBUTIONS

Concept: H.İ., B.S.Ş.; Design: H.İ., A.Ş., B.S.Ş.; Control: A.Ş., B.S.Ş.; Sources: H.İ.; Materials: - ; Data Collection and/or Processing: H.İ., A.Ş.; Analysis and/or Interpretation: H.İ., B.S.Ş.; Literature

Review: H.İ.; Manuscript Writing: H.İ.; Critical Review: A.Ş., B.S.Ş.; Other: -

CONFLICT OF INTEREST

The authors stated that there are no conflicts of interest regarding the publication of this article.

ETHICS COMMITTEE APPROVAL

The studies involving human participants were reviewed and approved by Bezmialem Vakif University Clinical Research Ethics Committee (05.04.2023/07-2). The patients/participants provided their written informed consent to participate in this study.

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