The Relationship Between Cognitive Function and Urinary Albumin Excretion in Type 2 Diabetic Patients

Tip 2 Diyabet Hastalarında Bilişsel İşlevler ve İdrar Albumin Atılımı Arasındaki İlişki

Barış AFŞAR[1]
Rengin ELSURER[1]
Tayfun EYİLETEN[2]

1 Zonguldak Ataturk State Hospital, Department of Nephrology, Zonguldak, Turkey
2 Gulhane Military Medical Academy, Department of Nephrology, Ankara, Turkey

ABSTRACT

OBJECTIVE: In the current study we aimed to analyze the relationship between urinary albumin excretion (UAE) with cognitive dysfunction in Turkish Type 2 diabetic patients

MATERIAL and METHODS: Patients with type 2 diabetes attending the Nephrology Clinic of Zonguldak Ataturk State hospital were included in the study. Medical history taking, physical examination, blood pressure measurements, biochemical analysis and collection of 24-hour urine specimens to determine creatinine clearance and UAE were performed. Cognitive function was evaluated by the Standardized Mini Mental State Examination (SMMSE).

RESULTS: In total, 195 type 2 diabetic patients whose mean SMMSE score was 26.6±2.2 were enrolled. The mean SMMSE scores of normoalbuminuric (71 patients), microalbuminuric (55 patients) and macroalbuminuric (69 patients) patients were 27.1 ±2.6, 26.7±1.9 and 26.0±1.9 respectively which were significantly different among the 3 groups (P: 0.009). Post-hoc analysis revealed that SMMSE scores were not significantly different between normoalbuminuric and microalbuminuric patients (P: 0.601) and between microalbuminuric and macroalbuminuric patients (P: 0.175). However, SMMSE scores significantly differed between normoalbuminuric and macroalbuminuric patients (P: 0.007). Stepwise multivariate linear regression analysis revealed that educational status (P<0.0001), age (P<0.0001), presence of cerebrovascular disease (P: 0.043), hemoglobin (P: 0.002), and logarithmically converted 24-hour UAE (P: 0.029) were found to be independently related with SMMSE scores.

CONCLUSION: 24-hour UAE is related with cognitive function in Turkish type 2 diabetic patients.

KEY WORDS: Cognitive function, Diabetes mellitus, Urinary albumin excretion, Albuminuria, Standardized mini mental state examination

ÖZ

AMAÇ: Bu çalışmamızda, Tip 2 diyabet hastalarında bilişsel işlevler ve idrar albumin atılımı arasındaki (İAA) ilişkiyi incelemeyi amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya Zonguldak Ataturk Devlet Hastanesi Nefroloji Kliniğine başvuran Tip 2 diyabetik hastalar alındı. Her hastanın tıbbi özgeçmişleri sorgulandı, fizik muayeneleri yapıldı, kan basınçları ölçüldü, biyokimyasal analizleri yapıldı ve kreatinin klirensi ve İAA hesaplamak üzere 24 saatlik idrarı toplandı. Hastaların bilişsel işlevler Standardize Mini Mental Test (SMMT) yöntemi ile belirlendi.

BULGULAR: Çalışmaya toplam 195 tip 2 diyabetik hasta alındı. Hastaların ortalama SMMT puanı 26,6±2,2 idi. Normoalbuminurik (71 hasta), mikroalbuminurik (55 hasta) ve makroalbuminurik (69 hasta) hastaların ortalama SMMT puanları sırasıyla 27,1±2,6, 26,7±1,9 ve 26,0±1,9 idi ve 3 grup arasındaki SMMT puanları birbirinden anlamlı olarak farklıydı (P: 0,009). Gruplar arası karşılaştırma sonucunda SMMT puanları normoalbuminurik ve mikroalbuminurik hastalarda (P: 0,601) ve mikroalbuminurik ve makroalbuminurik hastalarda (P: 0,175) farklı bulunmadı. Bununla birlikte SMMT puanları, normoalbuminurik ve makroalbuminurik hastalar arasında anlamlı olarak farklı bulundu (P: 0,007). Basamaklı doğrusal regresyon analizi sonucunda eğitim durumu (P< 0,0001), yaş (P< 0,0001), serebrovasküler hastalık (P: 0,043), hemoglobin (P: 0,002) ve logaritmik dönüşüm yapılmış 24 saatlik İAA SMMT ile bağımsız ilişkili olduğu gözlendi.

SONUÇ: Tip 2 diyabet hastalarında 24 saatlik İAA ile bilişsel işlev arasında ilişki vardır**.**

ANAHTAR SÖZCÜKLER: Bilişsel işlev, Diabetes mellitus, İdrar albumin atılımı, Albuminuri, Standardize mini mental test

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Correspondence Address:
Barış AFŞAR
Zonguldak Ataturk Devlet Hastanesi
Nefroloji Bölümü, Zonguldak, Turkey
Gsm : +90 532 470 51 90
E-mail : afsarbrs@yahoo.com

INTRODUCTION

Type 2 diabetes mellitus (DM) is a common condition and has shown to be associated with cognitive impairment. Studies suggest that cognitive impairment may be a complication experienced by persons with diabetes (1-4). However, these studies did not take into account possible differences in educational level and usually did not adjust for age, sex and comorbid conditions (2). Besides, exact mechanisms underlying cognitive dysfunction in diabetes mellitus remain unclear (5).

Persons with diabetes are at high risk for macro and microvascular damage leading to retinopathy, nephropathy, neuropathy, and cardiovascular and cerebrovascular diseases (1). With respect to brain function, atherosclerosis (macrovascular disease), which is highly prevalent in diabetic patients, may cause localized or global brain hypoperfusion and may lead to Alzheimer's disease, white matter lesions and cognitive dysfunction (6). Chronic hyperglycemia and hemodynamic changes in persons with type 2 diabetes may also lead to small vascular changes, including lacunar and microinfarcts, that are associated with cognitive impairment (7,8).

Less is known with respect to the relation between microvascular disease and cognitive dysfunction in type 2 diabetic patients. Diabetes mellitus is characterized by endothelial dysfunction. In turn, microalbuminuria (a sign of diabetic nephropathy) is related to endothelial dysfunction and is a risk factor for atherosclerosis. Thus, it is not surprising that diabetic atherosclerosis parallels diabetic glomerulosclerosis and is a very powerful risk factor for coronary heart disease and stroke in diabetic persons (9). Since atherosclerosis, as a macrovascular disease, is related with cognitive dysfunction, and both macrovascular and microvascular damage are closely related with each other, we hypothesized that 24-hour urinary albumin excretion (UAE), as a result of microvascular disease, may also be related with cognitive function in type 2 diabetic patients.

MATERIAL and METHODS

The current study was undertaken in the outpatient nephrology unit of Zonguldak Ataturk State Hospital between May 2008 and May 2010. The study was in accordance with the declaration of Helsinki and informed consent was obtained from all patients before enrollment. The study population comprised of type 2 diabetic patients. Exclusion criteria were type 1 diabetes mellitus, severe anemia, history of acute coronary syndrome, myocardial infarction, angina pectoris or coronary revascularization procedure (coronary stent replacement and coronary artery by-pass graft surgery) and a history of stroke, transient ischemic attack, carotid revascularization procedure, intermittent claudication, ischemic leg ulcer, peripheral revascularization or amputation for critical limb ischemia within last 3 months. Otherwise, patients with history of coronary artery disease, cerebrovascular disease and stroke were included. Patients included had no significant active neurological disease including Alzheimer's disease, psychiatric disease, including alcohol abuse, clinically diagnosed depression and anti-depressant medication usage, pulmonary, hepatic, autoimmune, endocrine or malignant disease. Patients who were illiterate were not included.

Patients attending our outpatient clinic underwent the following procedures; medical history taking, physical examination, office blood pressure (BP) measurements, cognitive function analysis (as detailed below), biochemical analysis and collection of 24-hour urine specimens to determine creatinine clearance and UAE.

Among sociodemographic and clinical characteristics age, gender, diabetes duration, levels of education, alcohol abuse (as determined by the presence of alcohol consumption), smoking status (smoker or nonsmoker), and presences of coronary artery, cerebrovascular and peripheral artery diseases, and diabetic retinopathy were recorded. The medications received (including oral hypoglycemic drugs, insulin, antihypertensives, statins, anticoagulant and antiplatelet agents) were also noted. Body mass index was calculated as the ratio of weight (in kilograms) to height squared (in square meters). Laboratory parameters including serum hemoglobin, glucose, albumin, high sensitive C-reactive protein, blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, thyroid stimulating hormone, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, and glycolysated hemoglobin (HbAlc) were measured.

Office Blood Pressure Measurement

Office BP measurements were performed using a mercury sphygmomanometer. Adequate sized cuffs (standard cuff of 23x12 cm or a large cuff of 34x15 cm) according to arm circumference were applied round the non-dominant arm. First and fifth phases of Korotkoff sounds were taken as the systolic and diastolic BPs respectively. The measurements were taken after the patients had rested for 10 minutes in the sitting position with the arm comfortably placed at the heart level. Two measurements were taken at 5-minute intervals. Each set of two measurements was averaged to give the office systolic and diastolic BPs. Clinical hypertension was defined as a BP ≥140/90 mmHg.

Measurement of Cognitive Function

The Standardized Mini Mental State Examination (SMMSE) was used for the analysis of cognitive function. The SMMSE scores range from 30 (unimpaired) to 0 (impaired) (10). It provides a global score of cognitive ability that correlates with function in activities of daily living. The SMMSE measures various domains of cognitive function including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression, and the ability to read and follow written instructions, write a sentence,

Table I: The demographic characteristics of 195 type 2 diabetic patients.

Parameter	***n=195***
Age (years) (mean±SD)	59.0 ± 10.2
Gender (male/female) (n)	84 / 111
Diabetes duration (months) (mean±SD)	125.2 ± 88.4
Primary school/ other	97 / 98
Body mass index (kg/m^2) (mean±SD)	29.3 ± 4.8
Smokers/non-smokers (n)	58 / 137
Coronary artery disease (present/absent) (n)	64 / 131
Cerebrovascular disease (present/absent) (n)	36 / 159
Peripheral artery disease (present/absent) (n)	24 / 171
Antihypertensive drug use (present/absent) (n)	123 / 72
Statin use (present/absent) (n)	105 / 90
Hypogylcemic drugs (n)	
None	24
Only insulin	113
Only oral hypoglycemic agents	38
Both insulin and oral hypoglycemic agents	20
Anticoagulant and Antiplatelet Drugs (n)	
None	113
Only warfarin	8
Only acetylsalicylic acid	66
Both warfarin and acetylsalicylic acid	8

construct a diagram, and follow a three-step verbal command. The SMMSE takes approximately 10 minutes to administer, provides a baseline score of cognitive function and pinpoints specific deficits that can aid in forming a diagnosis. The SMMSE is a reliable instrument that allows practitioners to accurately measure cognitive deficits and deterioration over time (11). The Turkish version of the SMMSE has been validated and shown to be reliable in the Turkish population (12).

Statistics

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., IL, USA). Data are shown as mean ± standard deviation, median, range and as a percentage (%). Results were considered statistically significant if two-tailed P was less than 0.05. Pearson's and Spearman's correlation coefficients were used where appropriate. Multivariate stepwise linear regression analyses were performed to assess the independent association of several variables with SMMSE score. The effects were measured by odds ratios and 95% confidence intervals based on logistic regression models. Since 24-hour UAE is not normally distributed, logarithmic conversion was performed before the analysis. Analysis of SMMSE scores between normoalbuminuric, microalbuminuric and macroalbuminuric patients were carried out by analysis of variance. For the post hoc analysis, Scheffe test was used. For the comparison of SMMSE scores between patients with and without diabetic nephropathy, we used Student t test.

RESULTS

A total of 300 patients were initially enrolled and the final study population was composed of 195 type 2 diabetic patients. The flow chart of the patient enrollment was shown in Figure 1. The demographic characteristics, laboratory parameters and BPs of 195 type 2 diabetic patients are shown in Table I and Table II, respectively. The mean SMMSE score was 26.6±2.2. According to the 24-hour UAE, 71 patients were normoalbuminuric (24-hour UAE is <30mg/day), 55 patients were microalbuminuric (24-hour UAE is between 30mg/day and 299.9 mg/day) and 69 patients were macroalbuminuric (24-hour UAE is ≥300 mg/day). In univariate correlation analysis, SMMSE scores were correlated with age (rho: -0.412, P <0.0001), creatinine (rho: -0.148, P: 0.039), blood urea nitrogen (rho: -0.192, P: 0.007), albumin (rho: +0.153, P: 0.033), systolic BP (rho: -0.153, P: 0.033), hemoglobin (rho: +0.244, P: 0.001) and uric acid (rho: -0.182, P: 0.012). In Pearson correlation analysis, SMMSE score was negatively correlated with log24-hour UAE (r: -0.202, P: 0.005) (Figure 2). Stepwise multivariate linear regression analysis was performed to assess the independent

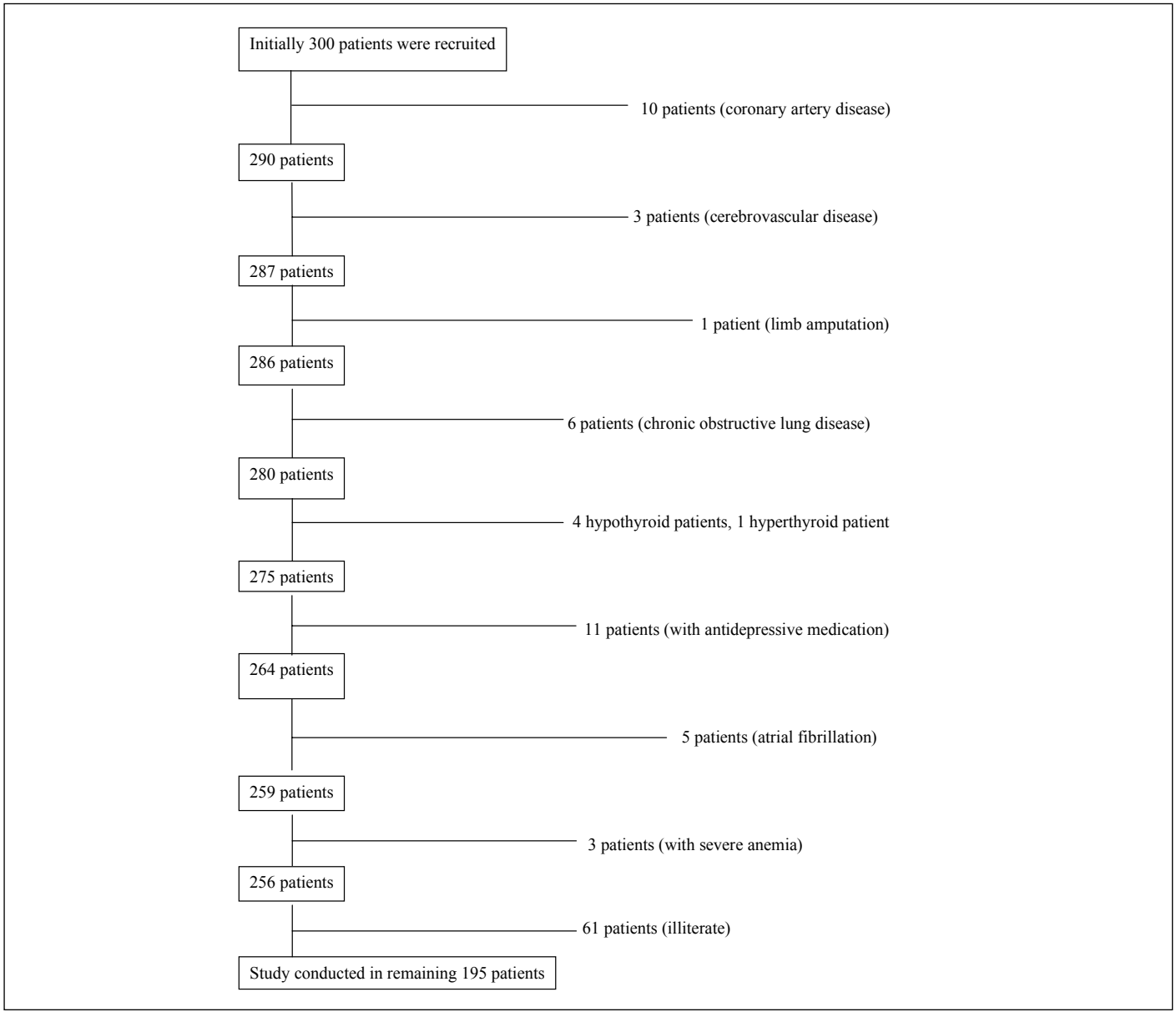

Figure 1: *The flow chart of patient enrollment.*

effects of several variables, including, gender, age, duration of diabetes, educational status (primary school graduate or higher school graduate), smoking status, body mass index, systolic and diastolic BPs, presence of coronary artery and cerebrovascular diseases, creatinine clearance, use of hypoglycemic agents (dichotomized to the presence of insulin use or not), statins and antihypertensive medication. Among laboratory parameters, fasting blood glucose, hemoglobin, HbA1c, high sensitive C-reactive protein and log24-hour UAE were included in the model. The linear regression analysis revealed that educational status, age, presence of cerebrovascular disease, hemoglobin and log24-hour UAE were found to be independently related with SMMSE scores (Table III).

The mean SMMSE scores of normoalbuminuric, microalbuminuric and macroalbuminuric patients were 27.1 ±2.6, 26.7±1.9 and 26.0±1.9, respectively and the mean SMMSE scores were significantly different among groups (P: 0.009). Post-hoc analysis revealed that SMMSE scores were not significantly different among normoalbuminuric and microalbuminuric patients (P: 0.601) and among microalbuminuric and macroalbuminuric patients (P: 0.175). However, SMMSE scores significantly differed between normoalbuminuric and macroalbuminuric patients (P: 0.007) (Figure 3).

With respect to diabetic retinopathy, 55 patients had known diabetic retinopathy, 26 patients had no retinopathy and in 114 patients data was not available regarding retinopathy.

Table II: The laboratory parameters and blood pressures of 195 type 2 diabetic patients.

Parameter	***n=195***
Hemoglobin (g/L) (mean±SD)	123.1.8 ± 19,5
Blood glucose (mmol/L) (mean±SD)	9.19 ± 3,5
Albumin (g/L) (mean±SD)	39.6 ± 6,4
Blood urea nitrogen (mmol/L) (mean±SD)	11.0 ± 6,7
Creatinine (μmol/L) (mean±SD)	154.2 ± 112,1
Sodium (mmol/L) (mean±SD)	138.9 ± 4,0
Potassium (mmol/L) (mean±SD)	4.7 ± 0,6
Calcium (mmol/L) (mean±SD)	2.28 ± 0,17
Phosphorus (mmol/L) (mean±SD)	1.23 ± 0,23
Uric acid (μmol/L)	371.8 ± 113,0
High sensitive C-reactive protein (mg/dl) (mean±SD)	1.38 ± 1,57
HbA1c (%)	7.95 ± 1,9
Total cholesterol (mmol/L) (mean±SD)	5.0 ± 1,4
LDL-C (mmol/L) (mean±SD)	2.9 ± 1,1
HDL-C (mmol/L) (mean±SD)	1.1 ± 0,3
Triglyceride (mmol/L) (mean±SD)	1.90 ± 0,98
Thyroid Stimulating hormone mU/L	1.88 ± 1,35
Clinic systolic blood pressure (mmHg) (mean±SD)	143.2 ± 16,5
Clinic diastolic blood pressure (mmHg) (mean±SD)	82.5 ± 10,6

SD; Standard deviation. **LDL-C;** Low-density lipoprotein cholesterol, **HDL-C;** low-density lipoprotein cholesterol.

Table III: Linear regression analysis of factors related with standardized mini mental state examination scores.

Parameter	**B**	**95% Confidence Interval**	***P***
Educational status (Elementary school vs. higher)	-1,370	-1,964 -(-) 0,776	<0,0001
Age	-0,07	-0,100 -(-) 0,039	<0,0001
Hemoglobin	0,025	0,009 - 0,040	0,002
Log24-hour UAE	-0,387	-0,734 -(-) 0,040	0,029
Presence of cerebrovascular disease	-0,788	-1,552 -(-) 0,024	0,043

UAE; *Urinary albumin excretion.*

Comparison of SMMSE scores in patients with and without retinopathy revealed that patients with diabetic retinopathy had lower SMMSE scores then patients without retinopathy (26.0±2.0 vs. 27.3±2.1, P: 0.012)**.** However, since we did not know the retinopathy status of the majority of our patients, we did not include this parameter in regression analysis.

DISCUSSION

In the current study, we found that age, hemoglobin, educational status, cerebrovascular disease and log24-hour UAE were independently related with cognitive function. To the best of our knowledge, our study is the first to examine the relationship of cognitive function with various parameters including UAE in the Turkish diabetic population.

We found an independent association between 24-hour UAE and cognitive function**.** Some other studies have also demonstrated a close relationship between UAE and cognitive dysfunction (13-17). Although these studies demonstrated a relationship between albuminuria and cognitive function, systematic examination of the relationship between diabetes and cognitive function is not usually evaluated in routine clinical care. Besides, the mechanism linking diabetes to impaired cognition remains unclear. One plausible explanation is that vascular

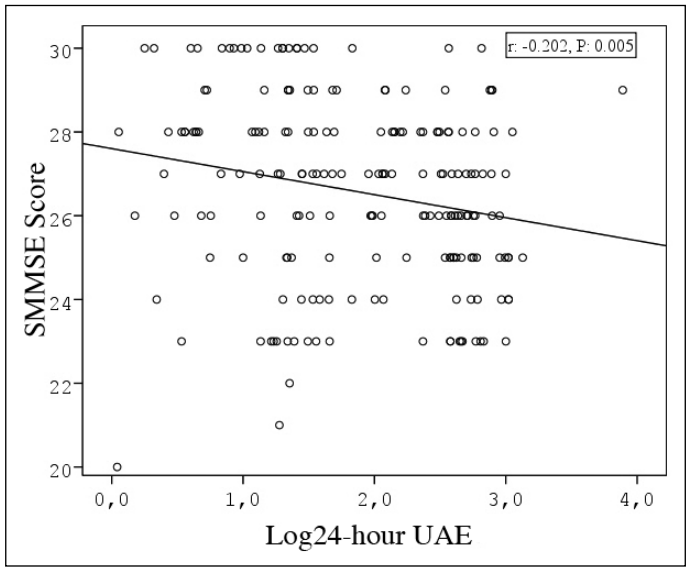

Figure 2: *The regression graphic of Standardized Mini Mental State Examination score and log24-hour urinary albumin excretion.*

(SMMSE; Standardized Mini Mental State Examination, UAE; Urinary albumin excretion).

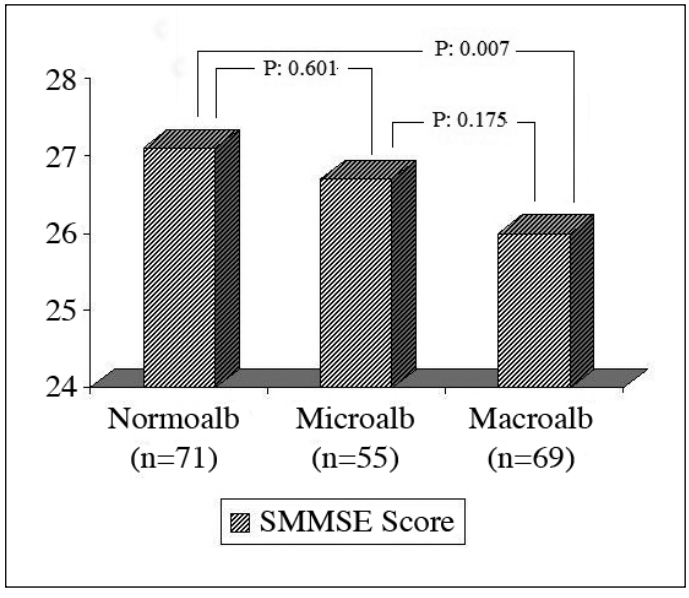

Figure 3: *Comparison of Standardized Mini Mental State Examination scores of normoalbuminuric, microalbuminuric and macroalbuminuric patients.*

(Normoalb; Normoalbuminuric, Microalb; Microalbuminuric, Macroalb; Macroalbuminuric).

factors may be playing a role. Diabetes is known to be associated with vascular disease and cerebrovascular pathology is thought to increase the likelihood of the clinical expression of neurologic disease (18). The pathogenetic mechanisms regarding UAE and cognitive function are even less clear but theories exist. It is well known that albuminuria is the result of endothelial damage in the kidney, which, in turn, is the result of microvascular disease. If one of the key mechanisms of brain microvascular disease is leakage of serum proteins into the brain extracellular space, in a fashion parallel to albuminuria that occurs in nephrosclerosis, then the extravasation of proteins both in kidneys and in brain could explain the relationship between UAE and cognitive function. Thus, it was concluded that albuminuria might be a useful screening test for generalized microvascular disease and, if detected, might reasonably prompt more intensive therapeutic efforts to forestall further endothelial dysfunction in the kidney, brain and elsewhere (19, 20).

In our study, we found that history of cerebrovascular disease was independently associated with cognitive dysfunction. Our findings are not novel and cerebrovascular disease is established risk factor for cognitive decline (21, 22). In a systemic meta-analysis, anemia was found to be related to cognitive dysfunction. It can be imagined that diagnosed anemia or low hemoglobin could impact on future cognitive impairment, either directly by reducing blood oxygen levels in the brain over a sustained period of time or possibly by lowering the threshold or reserve capacity such that an otherwise silent cerebrovascular accident (such as a small stroke or transient ischemic attack) has a greater impact on subsequent cognition (23). Supporting these hypotheses, our results showed that hemoglobin was positively associated with SMMSE scores in univariate and multivariate analyses.

We found no relationship between HbA1c levels and smoking status, and SMMSE scores, which are in accordance with previous findings (24,25). We also did not demonstrate any relationship between medication regimens of hypoglycemic drugs and cognitive function, similar to the results of Saczynski et al. (1).

Our study has limitations; the observational study design does not allow the ascertaining of causality. In addition, the cross-sectional design does not allow testing for temporal changes including the 24-hour UAE. . Although we recorded the vascular complications of DM, these were based on medical history and the data about diabetic retinopathy was not available for all patients. This issue may be especially important since some studies showed a relation of retinopathy with vascular brain lesions and cognitive impairment (26,27). Also, albuminuria and cognitive function may be related to one another through factors not measured in this study, such as increased levels of oxidative stress (28). Lastly depressive behaviour that may be related with SMMSE scores was not evaluated in our study.

Our study also has some strengths. Firstly, to the best of our knowledge, our study is unique since it is the first study regarding the cognitive function and related parameters in Turkish type 2 diabetic patients. Secondly, although the SMMSE is not the gold standard for the detection of cognitive dysfunction, it is easy to administer and provides a global score of cognitive ability

that correlates with function in activities of daily living (11). We evaluated many sociodemographic and laboratory factors in a combined fashion and we assessed the medications, degree of glycemic control and nephropathy in a relatively large number of patients.

In conclusion, 24-hour UAE is related with cognitive function in Turkish type 2 diabetic patients. Clinical trials are necessary to determine whether interventions targeting albuminuria can prevent cognitive decline in type 2 diabetic patients.

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