Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

RESEARCH ARTICLE

Çadırcı et al: Cognitive impairment and serum NPTX2 in DM

Serum NPTX2 and cognitive impairment in geriatric diabetes: A cross-sectional study

Kenan Çadırcı[1*], Muharrem Bayrak[1], Alev Lazoğlu Özkaya[2], Gamze Nur Yılmaz[3], Nur Pak[4], Büşra Karahan[1], Hilal Kiziltunc Ozmen[5]

[1]Department of Internal Medicine, Erzurum Faculty of Medicine, Health Sciences University, Erzurum, Türkiye

[2]Department of Biochemistry, Erzurum Faculty of Medicine, Health Sciences University, Erzurum, Türkiye

[3]Department of Child Health and Diseases Nursing, Institute of Health Sciences, Atatürk University, Erzurum, Türkiye

[4]Department of Internal Medicine Nursing, Institute of Health Sciences, Atatürk University, Erzurum, Türkiye

[5]Department of Radiation Oncology, Faculty of Medicine, Atatürk University, Erzurum, Türkiye

[*]Correspondence to Kenan Çadırcı: kenan.cadirci@sbu.edu.tr

DOI: https://doi.org/10.17305/bb.2025.12632

ABSTRACT

Cognitive impairment is an increasingly common complication of diabetes, yet its underlying pathophysiological mechanisms remain poorly understood. Neuronal pentraxin 2 (NPTX2), a recently identified synaptic biomarker linked to cognitive disorders, has not previously been examined in relation to cognitive function in geriatric individuals with diabetes. This cross-sectional study enrolled 90 participants—46 geriatric patients with diabetes and 44 age-matched non-diabetic controls. Demographic and clinical data were collected for all participants. After informed consent, cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). Serum NPTX2 levels were measured by ELISA. No significant differences were found between the diabetic and control groups in age, sex, education level, marital status, smoking history, comorbid conditions, or polypharmacy. However, the groups differed significantly in MoCA scores ($p < 0.001$), MMSE scores ($p = 0.028$), and NPTX2 levels ($p = 0.048$); the diabetic group showed lower cognitive scores and biomarker levels. NPTX2 levels correlated positively with MoCA and MMSE scores and negatively with diabetes duration, patient age, and the presence of microvascular complications. In conclusion, cognitive function was significantly lower in geriatric patients with diabetes than in controls, and serum NPTX2 levels were significantly associated with cognitive performance. These findings suggest a possible role for NPTX2 in diabetes-related cognitive decline and support further investigation of its utility within a broader biomarker panel.

Keywords: Diabetes mellitus, geriatric patients, cognitive dysfunction, neuronal pentraxin 2, NPTX2.

INTRODUCTION

Diabetes mellitus is a serious metabolic disorder characterized by chronic hyperglycemia and is traditionally associated with well-known microvascular and macrovascular complications [1,2]. However, advancements in diabetes management and the resulting increase in life expectancy have led to the emergence of a broader range of diabetes-related comorbidities beyond these classical complications. Recent literature increasingly highlights a heightened risk and burden of additional conditions in individuals with diabetes, including a greater incidence of certain cancers—particularly those of gastrointestinal and ovarian origin—increased susceptibility to infections, liver disease, and various functional impairments. Notably, growing evidence points to a strong association between diabetes and cognitive and affective disorders [3,4]. Scientific studies have increasingly reported cognitive impairments in diabetic patients, encompassing deficits in memory, attention, concentration, verbal fluency, complex motor skills, processing speed, and executive functioning [5,6].

Cognitive dysfunction, defined as a decline in one or more cognitive abilities, is a significant issue that negatively impacts quality of life by diminishing functional capacity across various domains. Early diagnosis and appropriate management of cognitive impairment may help slow its progression, thereby enhancing self-care abilities and overall quality of life in individuals with diabetes [7]. The relationship between diabetes and cognitive dysfunction is multifaceted and complex, with underlying mechanisms that have not yet been fully elucidated. However, key pathophysiological factors are believed to include disruption of synaptic mitochondrial homeostasis in the brain, driven by pathological processes such as hyperglycemia, oxidative stress, inflammation, insulin resistance, and the accumulation of advanced glycation end products (AGEs). These factors contribute to synaptic dysfunction and neuronal loss, forming the core mechanisms linking diabetes to cognitive decline [8].

Synaptic mitochondria play a crucial role in meeting the high energy demands necessary for synaptic transmission, which is fundamental to learning and memory formation [9,10]. These mitochondria are particularly vulnerable to damage induced by AGEs, and their dysfunction is a key contributor to age-related cognitive decline and synaptic degeneration [11]. Increasing evidence suggests that mitochondrial plasticity plays a critical role in synaptic transmission, including the synthesis and

storage of neurotransmitters, synaptic vesicle trafficking, neurotransmitter release into the synaptic cleft, and further recycling of neurotransmitters [12].

Neuronal pentraxins (NPTXs), recognized as potential biomarkers of synaptic dysfunction [13], comprise three protein families: NPTX1, NPTX2, and the neuronal pentraxin receptor (NPTXR). These proteins play key roles in neurotransmitter transmission, synaptic function regulation, synaptic plasticity, neuronal survival, and the modulation of excitatory synapses [14]. Synaptic plasticity, in particular, is critical for cognitive processes such as learning and memory [15]. There is also evidence that NPTXs are involved in intracellular processes, such as mitochondrial dynamics and trafficking, as well as neuronal apoptosis [13]. NPTX2 plays a role in forming and stabilizing excitatory synapses that contain AMPA glutamate receptors. It regulates the number of AMPA receptors at synapses and promotes their clustering. Thus, it has essential functions in regulating synaptic plasticity, neuronal survival, and excitatory synaptic activity in the central nervous system [16] and plays an important role in both developmental and adult synaptic plasticity [17]. These roles enable the precise control of learning, memory formation and storage, information processing, and other core neurological functions.

NPTX2 is a Ca^{2+}-dependent lectin that plays an important role in neurodevelopmental processes. This protein is also called neuronal activity-regulated pentraxin [18-20]. It is widely expressed in the brain, particularly in the hippocampus [18]. Parvalbumin (PV) interneurons are the most common interneuron subtype in the hippocampus. These GABAergic interneurons are crucial for maintaining an optimal balance of excitation and inhibition [13] NPTX2 binds to the GluA4 subunit of AMPA receptors in PV interneurons. This binding helps maintain the excitatory–inhibitory balance. NPTX deficiency can disrupt this balance, leading to impairments in learning and memory. Given its central involvement in these processes, NPTX2 has garnered increasing attention in recent years for its potential role in neurodegenerative, neuropsychiatric, and other neurological disorders. Numerous studies have investigated its role in the pathophysiology of several other neurological diseases, such as schizophrenia [18], neuropathic pain [19], vascular dementia [20], Alzheimer's disease [21], Parkinson's disease [22], bipolar disorder [23], postoperative delirium [24,25], epilepsy [26], amyotrophic lateral sclerosis, and

frontotemporal dementia [27], as well as its effect on impaired cognitive function in combination with these diseases.

Glutamate is a critical excitatory neurotransmitter in the mammalian and human central nervous systems. It also mediates neural activity via GluR [28], which is known to regulate insulin secretion from beta cells [29].

NPTX2, which functions via AMPA-type glutamate receptors in the brain, functions to regulate insulin secretion from the islets of Langerhans beta cells via the same receptors. It has been reported that NPTX2 mRNA expression is decreased in the pancreatic islets of patients with type 1 diabetes [30]. One study revealed that inhibiting LKB1, which inhibits 5'-adenosine monophosphate-activated protein kinase (AMPK) involved in cellular energy homeostasis, increased NPTX2 expression and glutamatergic signaling due to hyperplasia and increased the mass of pancreatic beta cells [31]. The present findings reveal an intricate, although not yet clearly defined, pathophysiological relationship between NPTX2, AMPA-type glutamate receptors, glutamate, neuronal plasticity, and insulin secretion from the pancreas. The unknown aspects of this relationship may constitute the unknown elements of the pathophysiological process between diabetes and the loss of cognitive function related to diabetes.

To the best of our knowledge, no studies have specifically investigated the role of NPTX2 in the cognitive dysfunction associated with diabetes. While a substantial body of research has examined cognitive impairment in diabetic patients, these studies have relied primarily on internationally validated cognitive assessment tools such as the MoCA and MMSE [32,33]. To date, no research has explored the use of molecular biomarkers to assess cognitive decline or elucidate the underlying mechanisms in this population. This study is therefore significant, as it is the first to evaluate the association between serum NPTX2 levels and cognitive performance in individuals with diabetes. Given the established role of NPTX2 in synaptic plasticity and its dysregulation in neurodegenerative diseases, it may also be implicated in the cognitive complications of diabetes. We hypothesize that reduced serum NPTX2 levels are associated with impaired cognitive function in older adults with type 2 diabetes and may serve as a potential biomarker for diabetes-related cognitive decline. Accordingly, the objective of this study was to investigate the relationship between serum NPTX2 concentrations and cognitive performance in elderly diabetic patients,

with the aim of identifying early indicators of cognitive impairment and potential targets for intervention.

MATERIALS AND METHODS

Study design and population

This study employed a single-center, descriptive, cross-sectional design. It was conducted in the diabetes and general internal medicine outpatient clinics of a university hospital in Erzurum, Türkiye, between June 2024 and January 2025. Erzurum, the third-largest province in the Eastern Anatolia region, has a population of approximately 763,320. The hospital, a major referral center in the region, comprises 1,042 beds, including 146 dedicated to geriatric patients. The study was conducted in accordance with the principles of the Declaration of Helsinki. All assessments were carried out through face–to–face interviews by a trained nurse to ensure consistency across evaluations and to obtain the most accurate and standardized data possible.

Study population

Men and women aged 65 and older who presented for routine check-ups and were either diagnosed with diabetes or identified as nondiabetic controls were included in the study. The inclusion criteria for participation were providing voluntary informed consent, the ability to read and write in Turkish, completion of at least five years of formal education, no hearing or speech impairments, and being 65 years of age or older. The exclusion criteria included a known diagnosis of any psychiatric or neurological disorder, current use of psychiatric medications, the presence of kidney or liver disease, inability to communicate or follow instructions, a history of brain surgery, evidence of focal brain lesions on neuroimaging, a history of head trauma, or current alcohol or substance dependence. Exclusion decisions were based on a comprehensive review of participants' medical records and brief clinical interviews conducted at enrollment. This approach was designed to minimize confounding effects from preexisting neuropsychiatric conditions, allowing the study to specifically evaluate the relationship between diabetes and cognitive function in the context of serum NPTX2 levels.

Demographics and clinical information of the participants

The medical records of all participants were reviewed to collect data on age, sex, education level, marital status, comorbidities, current medications, duration of illness, smoking history, body mass index (BMI), and blood pressure.

Neurological assessment

Application of neurocognitive tests

The montreal cognitive assessment (MoCA)

The Montreal Cognitive Assessment (MoCA), developed by Nasreddine et al. [34], is a brief yet comprehensive cognitive screening tool known for its high sensitivity and specificity, particularly in detecting early-stage cognitive impairment. It evaluates eight cognitive domains: attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score ranges from 0 to 30, with higher scores reflecting better cognitive performance.

Given that MoCA test outcomes may vary depending on factors such as age, cultural background, education level, adaptation, validity, and reliability, studies have been conducted on the use of the MoCA in Türkiye [35]. The original MoCA recommends a cutoff score of 26 to indicate normal cognition. However, the Turkish validation study, Selekler et al. [35], established a threshold of 21. In this study, scores of 21 or higher were considered normal, while scores below 21 suggested cognitive decline in the Turkish population.

The Mini Mental State Examination (MMSE) Test

Originally developed by Folstein et al. in 1975 [36], the Mini-Mental State Examination (MMSE) is a widely used screening tool designed for the rapid and practical assessment of cognitive function. It comprises 11 questions that evaluate five core cognitive domains: orientation, registration, attention and calculation, recall, and language. Like the MoCA, MMSE scores range from 0 to 30, with higher scores reflecting better cognitive performance. A validity and reliability study of the MMSE for the Turkish population, specifically for the detection of mild dementia in individuals with formal education, was conducted by Güngen et al. [37]. According to their findings, a score of 24 or above is considered indicative of normal cognitive

function in the Turkish population, whereas scores below 24 suggest cognitive impairment.

Measurements of serum NPTX2

Fasting blood samples were collected between 08:00 and 10:00 a.m., following a period of rest with the participants seated. Venipuncture was performed by experienced personnel via vacutainer tubes, and blood was drawn from the antecubital vein. For the measurement of serum NPTX2 levels, samples were placed in yellow-capped biochemistry tubes and allowed to clot at room temperature. The samples were then centrifuged at 3000 rpm for 10 min to separate the serum, which was subsequently stored at –80°C until analysis. Prior to analysis, the serum samples were thawed under appropriate conditions, and all the assays were performed in a single batch in the medical biochemistry laboratory of the same university hospital. NPTX2 concentrations were measured via a BT (China) ELISA kit (Human NPTX2, Catalog No. E4709Hu) and a Rel Assay automated ELISA reader (BiobaseBiodusty, Shandong, China) following the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation (CVs) were <8% and <10%, respectively, as reported by the manufacturer. The kit's detection range for NPTX2 was 0.05 to 20 ng/mL. ELISA was chosen because it is a widely accepted, gold standard and validated method for the quantitative detection of low-abundance proteins in serum, blood, plasma, and other body fluids. To reduce variability and nonspecific effects, all samples were analyzed in duplicate under identical conditions within a single assay batch. A box plot evaluation revealed that only three values (data not given) met the criteria for a mild outlier. However, these values were not removed because they were within the physiologically plausible range and did not violate the assumptions of normality. Three mild outliers (8.74, 9.21, and 12.67 ng/mL) in serum NPTX2 levels were identified based on the 1.5 × IQR criterion; these values were retained in the final analysis as they were within a biologically plausible range. Two of these participants were in the diabetic group, and one was non-diabetic.

Ethics statement

The study was approved by the Scientific Research Ethics Committee of Health Sciences University, Erzurum Medical Faculty (Decision No. BAEK-12-234). The

purpose of the research was clearly explained to all participants, and written informed consent was obtained from each individual prior to their inclusion in the study.

Statistical analysis

Statistical analyses were performed via the Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Using the G-Power 3.1.9.7 program (t test), since there was no reference article, the effect size was calculated at a large level* (Cohen's d = 0.8), $\alpha = 0.05$, power $(1-\beta) = 0.90$, and when evaluated as two-sided, the smallest sample size was calculated as a total of 68 participants, 34 in the control and patient groups [38]. Descriptive statistics, including means, standard deviations, and percentages, were used to summarize the data. The Kolmogorov–Smirnov test was used to assess the normality of the numerical variables. For comparisons between two independent groups, the Mann–Whitney U test was used for nonnormally distributed data. Differences in categorical variables between groups were analyzed via the Chi-square test. Spearman's correlation coefficients (r) were calculated to evaluate the relationships between numerical variables. All the results were interpreted within a 95% confidence interval, and statistical significance was defined as $p<0.05$.

RESULTS

Participants' baseline clinical characteristics

The sociodemographic and clinical characteristics of the study population are shown in Tables 1 and 2, respectively. Ninety individuals, 46 with type 2 diabetes and 44 controls, participated in the research. The diabetic group consisted of 22 (47.8%) men and 24 (52.2%) women, and the non-diabetic group consisted of 22 men (50%) and 22 (50%) women. The median (IQR) age of the diabetic group was 67.5 (65-75) years, and the median (IQR) BMI was 29.9 (26.6-33.9) kg/m², whereas the median (IQR) age of the control group was 68.5 (65-75) years, and the median (IQR) BMI was 26.5 (23.5-28.5) kg/m². BMI was significantly greater ($p<0.001$) in the diabetic group, while there were no significant differences between the groups in terms of age ($p=0.650$) or sex ($p=0.502$). The higher BMI observed in the diabetic patients compared to the non-diabetic patients may be attributed to insulin resistance, increased visceral fat accumulation, the weight-gain effects of certain antidiabetic

medications, and lifestyle factors such as reduced physical activity. In terms of education level, 67.4% of the diabetic group were educated at the primary school level or above (at least five years of education), 28.3% were educated at the middle school level, and 4.3% were educated at the university level or higher. The comparable values in the control group were 65.9%, 15.9%, and 18.2%, respectively, and no significant difference was detected between the groups. In terms of marital status, 74% of those in the diabetic group were married, and 26% were widowed, whereas 65.9% and 34.1% of those in the control group were married. The differences were not significant. From the perspective of accompanying comorbid diseases, the prevalence of hypertension was 76% in the diabetic group and 77% in the control group (p=0.547). The other prevalences were 30.5% and 34%, respectively, for COPD (p=0.442); 58.6% and 54.5%, respectively, for CAD (p=0.253); 34.7% and 29.5%, respectively, for CHF (p=0.380); and 30.4% and 25%, respectively, for AF (p=0.367). None of the differences were significant. Polypharmacy was used by 56.5% of the diabetic group and 50% of the control group, and this difference was also insignificant. To summarize, there were no differences between the two groups in terms of age, sex, educational level, marital status, smoking history, comorbid disease, or polypharmacy **(Tables 1 and 2).** The diabetic group also exhibited significantly higher systolic and diastolic blood pressure values compared to the non-diabetic group (SBP: p<0.001; DBP: p=0.016) (Table 2). The median (IQR) MoCA score was significantly greater in the control group (21 (16.2-23)) than in the diabetic group (12 (8-15)) (p<0.001). The median (IQR) MMSE score was significantly greater in the control group (21 (18-23)) than in the diabetic group (18 (13-23)) (p=0.028) **(Table 2).** The significantly higher MoCA and MMSE scores in non-diabetic patients may be explained by the absence of chronic hyperglycemia-related neurodegeneration, vascular complications, and insulin resistance—all of which contribute to cognitive decline in individuals with diabetes.

Diabetes-related characteristics of the patients

The diabetic group exhibited significantly higher systolic and diastolic blood pressure values compared to non-diabetic individuals **(Table 2)**. This is consistent with the known association between type 2 diabetes and elevated cardiovascular risk profiles.

Diabetes-related characteristics, such as the duration of diabetes, treatment and accompanying microvascular complications, were evaluated. The patients were classified into 4 groups according to the duration of diabetes: 0–5 years (3 patients), 6–10 years (15 patients), 11–15 years (22 patients), and >16 years (6 patients). For the treatment of diabetes, the patients were classified into 4 groups: lifestyle modification (3 patients), only oral diabetic drugs (8 patients), only insulin (20 patients), and insulin plus oral diabetic drugs (15 patients). When microvascular complications were evaluated, 21 patients had nephropathy, 20 patients had retinopathy, and 41 patients had neuropathy. The diabetes-related characteristics of the patients are presented in **Table 3**.

There were no significant differences between the groups in terms of TSH ($p=0.142$), vitamin B12 ($p=0.688$), eGFR ($p=0.306$) or creatinine ($p=0.704$) values. However, significant differences in fasting plasma glucose ($p<0.001$), blood hemoglobin A1c ($p<0.001$), high-density lipoprotein cholesterol ($p=0.014$), and triglyceride ($p<0.001$) levels were detected between the groups. NPTX2 levels also differed significantly ($p=0.048$). The laboratory findings of the study groups are shown in **Table 4.**

NPTX2 levels were positively correlated with MMSE ($r=0.235$, $p=0.026$) and MoCA scores ($r=0.242$, $p=0.022$) and negatively correlated with duration of diabetes ($r=-0.219$, $p=0.038$), patient age ($r=-0.289$, $p=0.006$), nephropathy ($r=-0.253$, $p=0.016$), retinopathy ($r=-0.281$, $p=0.007$), polypharmacy ($r=-0.279$, $p=0.008$), CHF ($r=-0.216$, $p=0.041$) and AF ($r=-0.283$, $p=0.007$) scores. The correlations of NPTX2 with the numerical variables are shown in **Table 5.** Although the correlation coefficient between NPTX2 and MoCA was relatively weak ($r \approx 0.24$), they reached statistical significance, suggesting that this relationship is unlikely to be due to chance. This may reflect the complex, multifactorial nature of diabetes-related cognitive decline, which arises from a combination of vascular, metabolic, and neuroinflammatory mechanisms. In such contexts, even biomarkers with modest effect sizes can provide clinically meaningful insights, particularly if they reflect specific aspects of the disease, such as synaptic dysfunction. It is also important to note that small but statistically significant correlations are frequently observed in early biomarker research and may still have diagnostic or prognostic value when considered alongside other clinical variables.

MoCA scores were positively correlated with MMSE (r=0.502, p<0.001), NPTX2 (r=0.242, p=0.022), and education levels (r=0.250, p=0.017) and negatively correlated with duration of diabetes (r=-0.546, p<0.001), patient age (r=-0.222, p=0.035), BMI (r=-0.279, p=0.008), fasting plasma glucose (r=-0.436, p<0.001), blood hemoglobin A1c (r=-0.471, p<0.001), triglycerides (r=-0.303, p=0.004), nephropathy (r=-0.335, p<0.001), retinopathy (r=-0.368, p<0.001), and neuropathy (r=-0.406, p<0.001). The correlations of the MoCA scores with the numerical variables are shown in **Table 6.**

MMSE scores were positively correlated with MoCA (r=0.502, p<0.001), NPTX2 (r=0.235, p=0.026), education level (r=0.260, p=0.013), and vitamin B12 (p=0.214, r=0.004) and negatively correlated with duration of diabetes (r=-0.217, p=0.040), patient age (r=-0.214, p=0.041), fasting plasma glucose (r=-0.235, p=0.026), blood hemoglobin A1c (r=-0.224, p=0.034), and polypharmacy (r=-0.258, p=0.014). The correlations between the MMSE score and the numerical variables are shown in **Table 7.**

DISCUSSION

The prevalence of diabetes is increasing rapidly worldwide. However, the availability of better therapeutic options, earlier detection of potential micro- and macrovascular complications, and more effective treatment have resulted in increased life expectancy. This longer life expectancy has itself led to new clinical problems, characterized by self-care problems and functional and cognitive impairment, in the literature. The impairment of cognitive function has an adverse impact on quality of life by reducing functional capacity. This has a major effect on diabetic patients, who must adapt to lifestyle changes and regularly use oral or injectable antidiabetic therapies for optimal treatment, which can potentially lead to severe complications such as hypoglycemia, treatment failure, and hospitalization. Current approaches, therefore, involve elucidating the pathophysiology of diabetes-related cognitive failure and identifying the molecular bases that might play a key role in that relationship. They also involve identifying drugs or approaches capable of positively impacting treatment in light of those molecular bases, determining accurate, early and consistent diagnostic methods and biomarkers, and establishing optimal approaches to complications that may arise [8,39,40].

According to National Diabetes Statistics Report data (2024), the proportion of adults with diabetes increases with age and currently stands at 29.2% of individuals aged 65 and over [41]. The American Diabetes Association recommends that diabetic individuals aged over also be screened for cognitive function loss at their first visit and annually thereafter [42]. Diabetic patients aged over 65 years were therefore included in this study because a potential loss of cognitive function might result in more severe outcomes associated with insufficient self-care and treatment.

This study included two groups, a diabetic group and a control group, both aged over 65 years, with no statistically significant differences in terms of age, sex, education level, marital status, smoking history, accompanying additional diseases, or polypharmacy use. Significant cognitive function loss, as determined via the MoCA and MMSE scores, was observed in the diabetic group. The current literature indicates that diabetes is a powerful risk factor for the development of cognitive function disorders [43,44]. The risk of dementia is reported to be between 1.46- and 2.48-fold greater in adults with type 2 diabetes mellitus than in the general population [45]. Similarly, the findings of the present study revealed a marked loss of cognitive function in diabetic geriatric patients. In addition to being used to diagnose and treat patients with diabetes [46-49], prediabetes [50,51], insulin resistance [52,53], and metabolic syndrome [54], which represent different stages of glucose metabolism disorders, are associated with pathological changes that might take place in regions of the brain associated with cognitive functions and poorer cognitive performance. There is even evidence that earlier-onset type 1 diabetes [55], hypoglycemic episodes that might develop during treatment [56], and glycemic fluctuations [57] are associated with poorer cognitive performance. We regard the fact that hypoglycemic episodes and glycemic fluctuations were not included in the evaluation as one of the limitations of this study.

Thyroid hormones and vitamin B12 play crucial roles in brain development and function by affecting processes such as neuron myelination and neurotransmitter synthesis [58,59]. Owing to the close association between vitamin B12 and thyroid hormone levels and neuropsychiatric symptoms and those linked to dementia [50,60] and the close relationship between creatinine elevation and poorer cognitive functions [61], care was taken in the present study to ensure that TSH, vitamin B12, and

creatinine levels were within normal limits. No significant difference was detected between the study groups in terms of any of these parameters.

The diagnostic evaluation of cognitive function in individuals with diabetes follows the same approach as in nondiabetic individuals. According to the American Diabetes Association guidelines, cognitive screening tools such as the MoCA and MMSE are recommended when dementia is suspected [62]. Both are internationally recognized and validated assessments. However, their effectiveness may be limited by the need for administration by trained professionals and by the literacy level of the patient. In the present study, efforts were made to enhance the reliability and standardization of the cognitive assessments. To achieve this goal, only participants with at least five years of formal education were included, and all tests were administered by trained professionals to ensure consistency and accuracy in the results.

An increasing number of studies have identified NPTX2 as a prognostic marker for cognitive decline associated with neurodegenerative, neuropsychiatric, and other neurological disorders [18,19,23,26]**.** Consistent with these findings, the present study demonstrated a significant difference in NPTX2 levels between the diabetic and control groups. Furthermore, NPTX2 levels were positively correlated with both MMSE and MoCA scores. While these associations were statistically significant, the correlation coefficients were modest, suggesting that NPTX2 may reflect only a partial contribution to the complex mechanisms underlying cognitive performance. Interestingly, NPTX2 and insulin play similar roles in maintaining normal synaptic structure and function. Both contribute positively to neuronal survival, synaptic plasticity, and cognitive processes such as learning and memory [63]. On the basis of these observations, we suggest that the cognitive decline observed in the diabetic group—alongside reduced NPTX2 levels—may be partially attributed to decreased insulin levels and/or impaired insulin function commonly observed in diabetes patients.

Patients with peripheral microvascular complications—particularly retinopathy and nephropathy—are at greater risk of cognitive decline than are those without such complications [64]. In the present study, correlation analysis was conducted to explore the relationships between diabetic microvascular complications and cognitive function. The results revealed negative correlations between MoCA scores and the presence of nephropathy, retinopathy, and neuropathy, which aligns with findings

reported in previous studies. In a study conducted by Öktem et al., in which diabetic and completely healthy controls were included with and without diabetic retinopathy, the MoCA scores were significantly lower in the retinopathy group than in the control group, and again, a significantly smaller gray matter volume was detected in the right insula in the retinopathy group than in the control group [65].

In this study, MoCA scores were negatively correlated with diabetes duration, fasting plasma glucose levels, and hemoglobin A1c (HbA1c) levels. These findings indicate that cognitive function declines with longer disease duration, older patient age, and poorer glycemic control. Consistent with previous research [66], our results underscore the progressive and detrimental impact of poorly controlled, long-term diabetes on cognitive performance.

It is challenging to directly compare our findings with those in the current literature, as, to the best of our knowledge, this is the first study to assess cognitive function using a biomolecular marker rather than relying solely on standardized questionnaires such as the MoCA and MMSE.

However, several limitations should be acknowledged. First, the study did not account for the potential impact of hypoglycemic episodes and glycemic fluctuations, both of which may influence cognitive outcomes. Second, the potential cognitive effects of different antidiabetic medications were not assessed on an individual basis. Third, the exclusion of participants with preexisting neurological or psychiatric conditions, although intended to reduce confounding, may also limit the applicability of the findings to the broader diabetic population, in which such comorbidities are common. These factors should be considered in future research to provide a more comprehensive understanding of the interactions among diabetes, cognitive function, and biomarkers such as NPTX2. In addition, NPTX2 is expressed not only in the central nervous system but also in pancreatic islet cells. Considering the potential influence of metabolic disorders such as diabetes, it is possible that serum NPTX2 levels reflect both central and peripheral sources. This should be taken into account when our results are interpreted.

CONCLUSION

This study is the first to evaluate the association between serum NPTX2 levels and cognitive performance in individuals with diabetes. The results of the MoCA and MMSE tests in this study demonstrated a decline in cognitive function among geriatric diabetic patients. Additionally, NPTX2 levels differed significantly between the diabetic and control groups. The relationship observed between NPTX2 levels and cognitive impairment in diabetic patients provides preliminary evidence for a possible role of this biomarker in the pathophysiology of diabetes-related cognitive decline. Further in-depth research into the molecular pathways through which NPTX2 may influence cognitive function is needed to determine its clinical significance and potential utility in diagnosis or monitoring. A clearer understanding of the role of NPTX2 could also support its use as a biomarker for diagnosis and progression prediction, complementing internationally recognized cognitive assessment tools. Therefore, when the pathophysiological role of NPTX2 levels in cognitive impairment in patients with diabetes is fully proven, the current biomarkers may guide both rapid and early diagnosis and the development of an effective treatment modality via NTPX2.

Conflits of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Data availability: The datasets used in the study are available from the corresponding author upon reasonable request.

Submitted: May 4, 2025

Accepted: July 16, 2025

Published online: July 22, 2025

REFERENCES

1. Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, et al. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. Signal Transduct Target Ther 2023; 10(8):152.
2. Barrett EJ, Liu Z, Khamaisi M, King GL, Klein R, Klein BEK, et al. Diabetic microvascular disease: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab 2017;102(12):4343-4410.
3. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nat Rev Endocrinol 2022;18(9):525-539.
4. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia 2019;62(1):3-16.
5. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. Endocr Rev 2008 ;29(4):494-511.
6. Cholerton B, Baker LD, Montine TJ, Craft S. Type 2 Diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectr 2016;29(4):210-219.
7. Subramanian M, Vasudevan K, Rajagopal A. Cognitive impairment among older adults with diabetes mellitus in Puducherry: A community-based cross-sectional study. Cureus 2021;13(1):e12488.
8. Aderinto N, Olatunji G, Abdulbasit M, Ashinze P, Faturoti O, Ajagbe A, et al. The impact of diabetes in cognitive impairment: A review of current evidence and prospects for future investigations. Medicine (Baltimore) 2023;102(43):e35557.
9. Luo JS, Ning JQ, Chen ZY, Li WJ, Zhou RL, Yan RY, et al. The role of mitochondrial quality control in cognitive dysfunction in diabetes. Neurochem Res 2022;47(8):2158-2172.
10. Henstridge CM, Pickett E, Spires-Jones TL. Synaptic pathology: A shared mechanism in neurological disease. Ageing Res Rev 2016; 28:72-84.
11. Samanta S, Akhter F, Xue R, Sosunov AA, Wu L, Chen D, et al. Synaptic mitochondria glycation contributes to mitochondrial stres and cognitive dysfunction. Brain 2025 ;148(1):262-275.

12. Sayehmiri F, Motamedi F, Batool Z, Naderi N, Shaerzadeh F, Zoghi A, et al. Mitochondrial plasticity and synaptic plasticity crosstalk; in health and Alzheimer's disease. CNS Neurosci Ther 2024; 30(8):e14897.

13. Gómez de San José N, Massa F, Halbgebauer S, Oeckl P, Steinacker P, Otto M. Neuronal pentraxins as biomarkers of synaptic activity: from physiological functions to pathological changes in neurodegeneration. J Neural Transm (Vienna) 2022;129(2):207-230.

14. Ansari U, Wen J, Syed B, Nadora D, Sedighi R, Nadora D, et al. Analyzing the potential of neuronal pentraxin 2 as a biomarker in neurological disorders: A literature review. AIMS Neurosci 2024;11(4):505-519.

15. Lamprecht R, LeDoux J. Structural plasticity and memory. Nat Rev Neurosci 2004; 5(1):45-54.

16. Ansari U, Wen J, Syed B, Nadora D, Sedighi R, Nadora D, et al. Analyzing the potential of neuronal pentraxin 2 as a biomarker in neurological disorders: A literature review. AIMS Neurosci 2024;11(4):505-519.

17. NPTX2 Modulator. https://www. alzdiscovery. org/uploads/ cognitive_vitality_media/ NPTX2-Modulator.pdf. Access Date: 27.05.2025

18. Göverti D, Büyüklüoğlu N, Kaya H, Yüksel RN, Yücel Ç, Göka E. Neuronal pentraxin-2 (NPTX2) serum levels during an acute psychotic episode in patients with schizophrenia. Psychopharmacology (Berl) 2022;239(8):2585-2591.

19. Wang R, Man Y, Zhou M, Zhu Y, Wang L, Yang J. Neuropathic pain-induced cognitive dysfunction and down-regulation of neuronal pentraxin 2 in the cortex and hippocampus. Neuroreport 2021;32(3):274-283.

20. Shao K,Shan S, Ru W, Ma C. Association between serum NPTX2 and cognitive function in patients with vascular dementia. Brain Behav 2020;10(10):e01779.

21. Xiao MF, Xu D, Craig MT, Pelkey KA, Chien CC, Shi Y, et al. NPTX2 and cognitive dysfunction in Alzheimer's disease. Elife 2017;6:e23798.

22. Nilsson J,Constantinescu J, Nellgård B, Jakobsson P, Brum WS, et al. Cerebrospinal fluid biomarkers of synaptic dysfunction are altered in Parkinson's disease and related disorders. Mov Disord 2023;38(2):267-277.

23. Knorr U, Simonsen AH, Nilsson J, Brinkmalm A, Zetterberg H, Blennow K, et al. Cerebrospinal fluid synaptic biomarker changes in bipolar disorder -A longitudinal case-control study. J Affect Disord2024;358:250-259.

24. Guo Z, Hong X, Wang X, Chen W, Guo Z. Association of reduced cerebrospinal fluid NPTX2 levels with postoperative delirium in patients undergoing knee/hip replacement: a prospective cohort study. Aging Clin Exp Res 2024;36(1):42.

25. Liu W, Wang Y, Jiang Y, Lu S, Zhu J, Tian Y, et al. Serum NPTX2 as a potential predictive biomarker for postoperative delirium in patients with acute type A aortic dissection. Neuropsychiatr Dis Treat 2024; 20:979-987.

26. Huang XF, Xu MX, Chen YF, Lin YQ, Lin YX, Wang F. Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalograms low wave/fast wave frequency ratio in epilepsy. World J Psychiatry 2023;13(10):714-723.

27. Krishnamurthy K, Pradhan RK. Emerging perspectives of synaptic biomarkers in ALS and FTD. Front Mol Neurosci2024;16:1279999.

28. Flores-Soto ME, Chaparro-Huerta V, Escoto-Delgadillo M, Vazquez-Valls E, González-Castañeda RE, Beas-Zarate C. Structure and function of NMDA-type glutamate receptor subunits. Neurologia 2012; 27(5):301-10. Spanish.

29. Palazzo E, Marabese I, Ricciardi F, Guida F, Luongo L, Maione S. The influence of glutamate receptors on insulin release and diabetic neuropathy. Pharmacol Ther 2024; 263:108724.

30. Wald L. Exploration of NPTX2 in islets of Langerhans. UF Journal of Undergraduate Research. 2020, Vol 21 Issue. 2.

31. Kone M, Pullen TJ, Sun G, Ibberson M, Martinez-Sanchez A, Sayers S, et al. LKB1 and AMPK differentially regulate pancreatic β-cell identity. FASEB J 2014;28(11):4972-85.

32. Malekian N, Hosseini SR, Moudi S, Bayani MA, Kheirkhah F, Bijani A, et al. Type 2 diabetes mellitus and cognitive function in Elderly People. Iran J Psychiatry Behav Sci 2018: e9494.

33. Gokce S, Barutcu CD. Evaluation of cognitive functions of individuals older than 65 with diagnosis of diabetes. Am J Alzheimers Dis Other Demen 2019;34(3):171-175.

34. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-9.

35. Selekler K, Cangoz B, Uluc S. Power of discrimination of Montreal Cognitive Assesment (MOCA) scale in Turkish patients with mild cognitive impairment and Alzheimer's disease. Turkish J Geriatr 2010;13(3):166-171.

36. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-98.

37. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Reliabilityandvalidity of thestandardized Mini Mental State Examination in the diagnosis of mild dementia in Turkish population. Turk PsikiyatriDerg 2002 Winter;13(4):273-81. (in Turkish)

38. Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates;1988

39. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and cognitive impairment. Curr Diab Rep 2016;16(9):87.

40. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol 2015;14(3):329-40.

41. National Diabetes Statistics Report. Available from: https://www.cdc.gov/diabetes/php/data-research/index.html. 2024. Access Date: 07.03.2025.

42. American Diabetes Association. *Standards of Care in Diabetes-2023* Abridged for Primary Care Providers. Clin Diabetes, 2022; 41(1):4-31. Erratum in: Clin Diabetes. 2023;41(2):328.

43. Nagasawa K, Matsumura K, Uchida T, Suzuki Y, Nishimura A, Okubo M, et al. Global cognition and executive functions of older adults with type 1 diabetes mellitus without dementia. J Diabetes Investig 2024;15(7):922-930.

44. Xue M, Xu W, Ou YN, Cao XP, Tan MS, Tan L, et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res Rev 2019;55:100944.

45. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012; 42(5):484-91.

46. Callisaya ML, Beare R, Moran C, Phan T, Wang W, Srikanth VK. Type 2 diabetes mellitus, brain atrophy and cognitive decline in older people: a longitudinal study. Diabetologia 2019;62(3):448-458.

47. Roberts RO, Knopman DS, Przybelski SA, Mielke MM, Kantarci K, Preboske GM, et al. Association of type 2 diabetes with brainatrophy and cognitive impairment. Neurology 2014;82(13):1132-41.

48. Groeneveld O, Reijmer Y, Heinen R, Kuijf H, Koekkoek P, Janssen J, et al. Brain imaging correlates of mild cognitive impairment and early dementia in patients with type 2 diabetes mellitus. NutrMetab Cardiovasc Dis 2018;28(12):1253-1260.

49. Li M, Huang L, Yang D, Luo C, Qin R, Zhang B, et al. Atrophy patterns of hippocampal subfields in T2DM patients with cognitive impairment. Endocrine 2020 ;68(3):536-548.

50. Dong S, Dongwei L, Zhang J, Liang J, Sun Z, Fang J. Individuals in the prediabetes stage exhibit reduced hippocampal tail volume and executive dysfunction. Brain Behav 2019;9(8):e01351.

51. Tatsuo S, Watanabe K, Ide S, Tsushima F, Tatsuo S, Matsuzaka M, et al. Association of prediabetes with reduced brain volume in a general elderly Japanese population. EurRadiol 2023; 33(8):5378-5384.

52. Willette AA, Xu G, Johnson SC, Birdsill AC, Jonaitis EM, Sager MA, et al. Insulin resistance, brain atrophy, and cognitive performance in late middle-aged adults. Diabetes Care 2013;36(2):443-9.

53. Benedict C, Brooks SJ, Kullberg J, Burgos J, Kempton MJ, Nordenskjöld R, et al. Impaired insulin sensitivity as indexedbythe HOMA score is associatedwithdeficits in verbalfluencyand temporal lobegraymattervolume in theelderly. Diabetes Care 2012;35(3):488-94.

54. Qureshi D, Topiwala A, Al Abid SU, Allen NE, Kuźma E, Littlejohns TJ. Association of metabolic syndrome with neuro imaging and cognitive outcomes in the UK Biobank. Diabetes Care 2024;47(8):1415-1423.

55. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol 2008;7(2):184-90.

56. Abdelhafiz AH, Sinclair AJ. Cognitive frailty in older people with type 2 diabetes mellitus: the central role of hypoglycemia and the need for prevention. Curr Diab Rep 2019;19(4):15.

57. Yang W, Si SC, Luo HY, Ma YX, Zhao H. Cognitive impairment and hippocampal degeneration in aged rat models of type 2 diabetes with induced glycemic fluctuation: A pilot study. Brain Res. 2025;1850:149452.

58. Alšauskė SV, Liseckienė I, Verkauskienė R. The association of thyroid disease with risk of dementia and cognitive impairment: A systematic review. Medicina (Kaunas) 2024 ;60(12):1917.

59. Venkatramanan S, Armata IE, Strupp BJ, Finkelstein JL. Vitamin B-12 and cognition in children. Adv Nutr 2016;7(5):879-88.

60. Liao Y, Zhang H, Zhang Y, Kan CN, Chia RSL, Chai YL,et al. The protective effect of vitamin B12 on neuropsychiatric symptoms in dementia-free older adults in a multi-ethnic population. Clin Nutr2025;44:25-32.

61. Bobot M, Burtey S. New insights into mechanisms underlying cognitive impairment in chronic kidney disease. Kidney Int 2024;106(6):1020-1022.

62. American Diabetes Association Professional Practice Committee. 13. Older Adults: Standards of Care in Diabetes-2025. Diabetes Care 2025; 48(Supplement_1):S266-S282.

63. Potenza MA, Sgarra L, Desantis V, Nacci C, Montagnani M. Diabetes and Alzheimer's disease: might mitochondrial dysfunction help deciphering the common path? Antioxidants (Basel) 2021;10(8):1257.

64. Yen YH, Yen FS, Ko FS, Wei JC, Huang Y, Yu TS, et al Microvascular disease and its association with dementia in patients with type 2 diabetes: A nationwide cohort study in Taiwan. Diabetes Obes Metab 2024;26(11):5399-5407.

65. Oktem EO, Sayman D, Ayyildiz S, Oktem Ç, Ipek L, Ayyildiz B, et al. Cognitive function deficits associated with type 2 diabetes and retinopathy: volumetric brain MR imaging study. Brain Behav 2025; 15(3):e70387.

66. Eugenia AO, Sani AF, Susanto H, Prajitno JH. Poor glycemic control is correlated with reduced cognitive function in type 2 diabetes mellitus patients. Biomolecular and Health Science Journal (BHSJ) 2022; 5(1), 1–5.

TABLES AND FIGURES WITH LEGENDS

Table 1. Comparison of the sociodemographic characteristics of the non-diabetic patients and diabetic patients

Variables	Group			*p* value
	Non-diabetic patients (*n*=44)	Diabetic patients (*n*=46)	Overall (*n*=90)	
Demographic Characteristics				
Age (year), median (IQR)	68.5 (65-75)	67.5 (65-75)	68 (65-75)	0.650
Sex				
Men, *n* (%)	22 (50)	22 (47.8)	44 (100)	
Women, *n* (%)	22 (50)	24 (52.2)	46 (100)	0.502
BMI (kg/m²), median (IQR)	26.5 (23.5-28.5)	29.9 (26.6-33.9)	27.75 (24.65-31.13)	<0.001
Educational level				
Primary school or above (at least>5 year), *n* (%)	29 (65.9)	31 (67.4)	60 (66.7)	
Middle school, *n* (%)	7 (15.9)	13 (28.3)	20 (22.2)	0.292
High school or above, *n* (%)	8 (18.2)	2 (4.3)	10 (11.1)	
Marital status				
Married, *n* (%)	29 (65.9)	34 (74)	63 (70)	
Separated or divorced, *n* (%)	0	0	0	
Widowed, *n* (%)	15 (34.1)	12 (26)	27 (30)	0.275
Never married, *n* (%)	0	0	0	
Smoking history				
Smoker, *n* (%)	14 (31.8)	15 (32.6)	29 (32.2)	
Nonsmoker, *n* (%)	23 (52.3)	24 (52.2)	47 (52.2)	0.97
Ex-smoker, *n* (%)	7 (15.9)	7 (15.2)	14 (15.6)	

BMI: Body mass index. **'Overall'** refers to pooled data from both non-diabetic and diabetic patients.

Table 2. Comparison of the clinical characteristics of the non-diabetic and diabetic patients

Variables	Group			*p* value
	Non-diabetic patients (*n*=44)	Diabetic patients (*n*=46)	Overall (*n*=90)	
Type of comorbid disease				
Hypertension, *n* (%)	34 (77)	35 (76)	69 (76.6)	0.547
COPD, *n* (%)	15 (34)	14 (30.5)	29 (32.2)	0.442
CAD, *n* (%)	24 (54.5)	27 (58.6)	51 (56.6)	0.253
CHF, *n* (%)	13 (29.5)	16 (34.7)	29 (32.2)	0.380
AF, *n* (%)	11 (25)	14 (30.4)	25 (27.7)	0.367
Polypharmacy, *n* (%)	22 (50)	26 (56.5)	48 (53.3)	0.342
Peripheral artery disease	4 (9.1)	1 (2.1)	5 (5.6)	0.167
Tension arterial				
Systolic Blood Pressure (mm Hg) median (IQR)	128 (124-132)	131.5 (128-134)	129 (127-132)	**<0.001**
Diastolic Blood Pressure (mm Hg) median (IQR)	86.5 (83-89)	87 (84-92)	87 (84-91)	**0.016**
MoCA median (IQR)	21 (16.2-23)	12 (8-15)	15 (10.75-21)	**<0.001**
MMSE median (IQR)	21 (18-23)	18 (13-23)	19.5 (15.75-23)	**0.028**

COPD: Chronic obstructive pulmonary disease; **CAD**: Coronary artery disease; **CHF**: Congestive heart failure; **AF**: Atrial fibrillation; **MoCA**: Montreal cognitive assessment; **MMSE**: Mini-mental state examination. '**Overall'** refers to pooled data from both non-diabetic and diabetic patients.

Table 3. Diabetes-related characteristics of diabetic patients

Variables	Diabetic patients (*n*=46)
Duration of diabetes	
0-5 year, *n* (%)	3 (6.5)
6-10 year, *n* (%)	15 (32.6)
11-15 year, *n* (%)	22 (47.9)
>16 year, *n* (%)	6 (13)
Treatment of diabetes	
Lifestyle modification, *n* (%)	3 (6.5)
Oral medications only, *n* (%)	8 (17.4)
Insulin only, *n* (%)	20 (43.5)
Oral medications+ insulin, *n* (%)	15 (32.6)
Microvascular complications	
Nephropathy, *n* (%)	21 (45.6)
Retinopathy, *n* (%)	20 (43.4)
Neuropathy, *n* (%)	41 (89.1)

Table 4. Laboratory findings of the study groups [median, (IQR)]

Variables	Groups		Overall (*n*=90)	*p* value
	Diabetic patients	Non-diabetic patients		
	PR (%95 Cl)	PR (%95 Cl)	PR (%95 Cl)	
NPTX2 (ng/ml)	1.15 (0.81-1.58)	1.41 (1.03-2.45)	1.29 (0.88-1.82)	**0.048**
Fasting Plasma Glucose (mg/dl)	176.5 (124-242.2)	84.5 (78-100.5)	112 (84-180)	**<0.001**
Blood hemoglobin A1c (%)	9.2 (7.5-11)	5.7 (5.5-5.9)	6.35 (5.67-9.25)	**<0.001**
Blood creatinine (mg/dl)	0.92 (0.76-1.19)	0.92 (0.74-1.26)	0.92 (0.75-1.22)	0.704
eGFR (mL/min/1,73 m²)	82.5 (54-101.6)	81.8 (50.3-88.5)	82.2 (53.2-96.2)	0.306
Sodium (mmol/L)	139 (136-141)	141 (139-142)	139 (137-142)	0.148
Potassium (mmol/L)	4.3 (3.6-4.6)	4.2 (3.7-4.4)	4.3 (3.6-4.6)	0.455
Calcium (mg/dL)	9.25 (8.8-9.8)	9.4 (8.7-9.7)	9.4 (8.8-9.8)	0.954
Albumin (g/L)	40.5 (35.7-42)	39 (35.2-42)	39.5 (35.75-42.0)	0.379
Low density lipoprotein Cholesterol (mg/dl)	120 (89-145)	110.5 (87.2-134.2)	117.5 (88-140.2)	0.696
High density lipoprotein cholesterol (mg/dl)	37.8 (31.3-44.6)	43.5 (35.3-52.1)	41.3 (33.6-50.8)	**0.014**
Triglycerides (mg/dl)	150 (104.5-241.5)	94.5 (81.7-133)	121 (87-175)	**<0.001**
Total cholesterol (mg/dl)	180 (145.7-217.7)	176.5 (152.2-220.2)	179 (147.5-218.7)	0.886

TSH (mlU/L)	1.23 (0.87-1.82)	1.16 (0.61-1.9)	1.20 (0.7-1.8)	0.142
Vitamin B12 (pg/ml)	339.5 (269.7-398.7)	315.5 (252.2-376.7)	326 (259-389)	0.688
Ferritin (ng/ml)	86.4 (27.6-156.4)	62.3 (23.6-98.2)	77.6 (24.9-122)	0.098
25-hidroksi vitamin D (ng/ml)	17.3 (12.6-30.8)	13.6 (11.2-25.1)	15.4 (11.6-28.1)	0.169

NPTX2: Neuronal pentraxin 2; **eGFR:** Estimated glomerular filtration rate; **TSH:** Thyroid-stimulating hormone; **PR:** Percentile range. 95% confidence intervals (CI) are shown. **'Overall'** refers to pooled data from both non-diabetic and diabetic patients.

Table 5. Correlation of the NPTX2 with numerical variables

Variables	r	*p*
MMSE	0.235	0.026
MoCA	0.242	0.022
Duration of diabetes (year)	-0.219	0.038
Age (year)	-0.289	0.006
Nephropathy	-0.253	0.016
Retinopathy	-0.281	0.007
Polypharmacy	-0.279	0.008
CHF	-0.216	0.041
AF	-0.283	0.007

MMSE: Mini-mental state examination; **MoCA**: Montreal cognitive assessment; **CHF:** Chronic heart failure; **AF:** Atrial fibrillation.

Table 6. Correlation of the MoCA score with numerical variables

Variables	r	*p*
MMSE	0.502	<0.001
NPTX2 (ng/ml)	0.242	0.022
Duration of diabetes (year)	-0.546	<0.001
Education level	0.250	0.017
Age (year)	-0.222	0.035
BMI (kg/m²)	-0.279	0.008
Fasting plasma glucose (mg/dl)	-0.436	<0.001
Blood hemoglobin A1c (%)	-0.471	<0.001
Triglycerides (mg/dL)	-0.303	0.004
Nephropathy	-0.335	<0.001
Retinopathy	-0.368	<0.001
Neuropathy	-0.406	<0.001

MMSE: Mini-mental state examination; **NPTX2:** Neuronal pentraxin 2; **BMI:** Body mass index.

Table 7. Correlation of the MMSE score with numerical variables

Variables	r	*p*
MoCA	0.502	<0.001
NPTX2	0.235	0.026
Education level	0.260	0.013
Vitamin B12 (pg/ml)	0.214	0.004
Duration of diabetes (year)	-0.217	0.040
Age (year)	-0.214	0.041
Fasting plasma glucose (mg/dl)	-0.235	0.026
Blood hemoglobin A1c (%)	-0.224	0.034
Polypharmacy	-0.258	0.014

MoCA: Montreal cognitive assessment; **NPTX2:** Neuronal pentraxin 2.