Alpha Psychiatry

Alpha Psychiatry **2026**; 27(6): 48990
https://doi.org/10.31083/AP48990

Original Article

Vascular Growth Factors and Cognitive Performance in Patients With Comorbid Type 2 Diabetes and Major Depressive Disorder: A Cross-Sectional Study

Dan Yu[1], Mei Yang[2], Li Shi[3], Na Li[1,*]

[1]Department of Psychiatry, The First Affiliated Hospital of Kunming Medical University, 650032 Kunming, Yunnan, China
[2]Department of Psychiatry, Xiangyang Anding Hospital, 441022 Xiangyang, Hubei, China
[3]Department of Endocrinology, The First Affiliated Hospital of Kunming Medical University, 650032 Kunming, Yunnan, China
*Correspondence: phoebe11@sina.com (Na Li)
Academic Editor: Francesco Bartoli
Submitted: 10 December 2025 Revised: 26 May 2026 Accepted: 10 June 2026 Published: 9 November 2026

Abstract

Background: Lower cognitive performance is common in patients with type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD), and is more severe in individuals with comorbid T2DM and MDD (TD). Vascular dysfunction may play a key role in the lower cognitive performance associated with both disorders. This study aimed to investigate the associations of serum vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) with poorer cognitive performance, and to further explore the role of vascular growth factors in patients with comorbid T2DM and MDD. **Methods:** Demographic characteristics, including age, sex, and other baseline variables, were recorded for all participants. Cognitive function was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Serum VEGF and bFGF levels were measured using enzyme-linked immunosorbent assay (ELISA) and then statistically compared across groups. Partial correlation analyses were performed with adjustment for relevant confounding variables to examine the associations between serum vascular growth factor levels and RBANS scores. Binary logistic regression analysis was performed to identify potential risk factors associated with TD. **Results:** A total of 169 participants were enrolled, including 32 healthy controls (HCs), 46 patients with MDD, 49 patients with T2DM, and 42 patients with comorbid T2DM and MDD (TD). Participants in the TD group exhibited poorer cognitive performance across all RBANS domains relative to HCs and T2DM, and lower visuospatial scores relative to MDD. In the TD group, serum VEGF levels were significantly elevated relative to HCs, while serum bFGF levels were higher than those in both HCs and MDD groups. Across the whole study cohort (n = 169), serum VEGF levels were significantly negatively correlated with the RBANS total score ($r = –0.241$, $p = 0.002$), delayed memory ($r = –0.256$, $p = 0.001$), language ($r = –0.326$, $p < 0.001$) and visuospatial scores ($r = –0.234$, $p = 0.002$). **Conclusions:** Serum VEGF and bFGF levels were elevated, accompanied by poorer cognitive performance, in patients with comorbid T2DM and MDD. Furthermore, increased serum VEGF levels were associated with lower cognitive performance in the overall study population.

Keywords: type 2 diabetes mellitus; major depressive disorder; vascular endothelial growth factor A; fibroblast growth factor 2; comorbidity; cognitive performance

Main Points

1. In this cross-sectional study, patients with comorbid type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) exhibited lower cognitive performance.

2. Serum vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) levels were significantly increased in patients with comorbid T2DM and MDD, and VEGF levels demonstrated weak to moderate inverse correlations with cognitive performance across the full study cohort.

3. Multivariate logistic regression (adjusted for age, sex, and waist circumference) indicated that VEGF and bFGF were significantly associated with comorbid status, albeit with very small effect sizes (OR ≈ 1.002–1.016).

4. Serum VEGF and bFGF demonstrated limited diagnostic utility for comorbid status (AUC 0.66–0.72) and are unsuitable as standalone diagnostic or predictive tools.

1. Introduction

Major depressive disorder (MDD) is now diagnosed in over 300 million people worldwide, and clinically characterized by depressed mood, reduced interest, and delayed thinking and behavior [1,2]. Studies have demonstrated that cognitive impairment, which gradually progresses from initial memory decline to ultimately dementia, should be recognized as one of the core symptoms of MDD [3,4,5]. The biological mechanisms underlying MDD and its associated cognitive impairment remain unclear, but may include neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis overactivation, amyloid-β and tau pathology and cerebrovascular dysfunction [6,7,8,9]. The role of vascular damage and vascular disease is gradually being emphasized. Studies have confirmed the association of microvascular dysfunction with a persistent depressive state [10]. As vascular endothelial dysfunction improves, patients with

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MDD can gradually gain relief from depressive symptoms [11]. In MDD, it has been shown that poorer cognitive function is also associated with more severe microvascular dysfunction [12].

Type 2 diabetes mellitus (T2DM) is a metabolic disease manifested predominantly as elevated blood glucose [13]. The cognitive impairment that occurs in patients with T2DM is increasingly recognized as an important complication of T2DM [14]. Currently, the mechanisms of cognitive dysfunction in T2DM remain unclear. Majority of existing studies have concentrated on the metabolic disorders, cerebral insulin resistance, accumulation of glycosylation end-products, inflammation, neurodegeneration, and mechanisms of vascular dysfunction [15,16,17,18]. Among the above mechanisms, the role of vascular risk factors and vascular damage in cognitive dysfunction in T2DM has been gradually emphasized. Microvascular dysfunction in T2DM due to hyperglycemia and glucose fluctuations can induce upregulation of pro-inflammatory cytokines in vascular endothelial cells, leading to vascular endothelial dysfunction [19,20]. T2DM is frequently accompanied by vascular risk factors including hypertension, obesity and dyslipidemia. Together with insulin pathway abnormalities, hyperglycemia, glucose fluctuations and chronic inflammation, these factors induce microvascular dysfunction, thereby leading to cerebral hypoperfusion, neuronal hypoxia and subsequent cognitive dysfunction [21,22,23].

Beyond the established associations of microvascular dysfunction with MDD and T2DM separately, an emerging neurobiological framework suggests that glymphatic system impairment may serve as a common pathway linking vascular pathology to cognitive and affective symptoms. Microvascular endothelial dysfunction impairs the efficiency of glymphatic transport, leading to compromised glymphatic clearance, accumulation of neurotoxic and inflammatory substrates, and subsequent exacerbation of neuroinflammation, synaptic dysfunction, and cognitive decline [24]. The normal expression of vascular growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), is particularly important in the function and regulation of the vascular endothelium. VEGF family of cytokines plays a key role in neovascularization and lymphangiogenesis [25]. bFGF is a member of the fibroblast growth factor family, and the se-

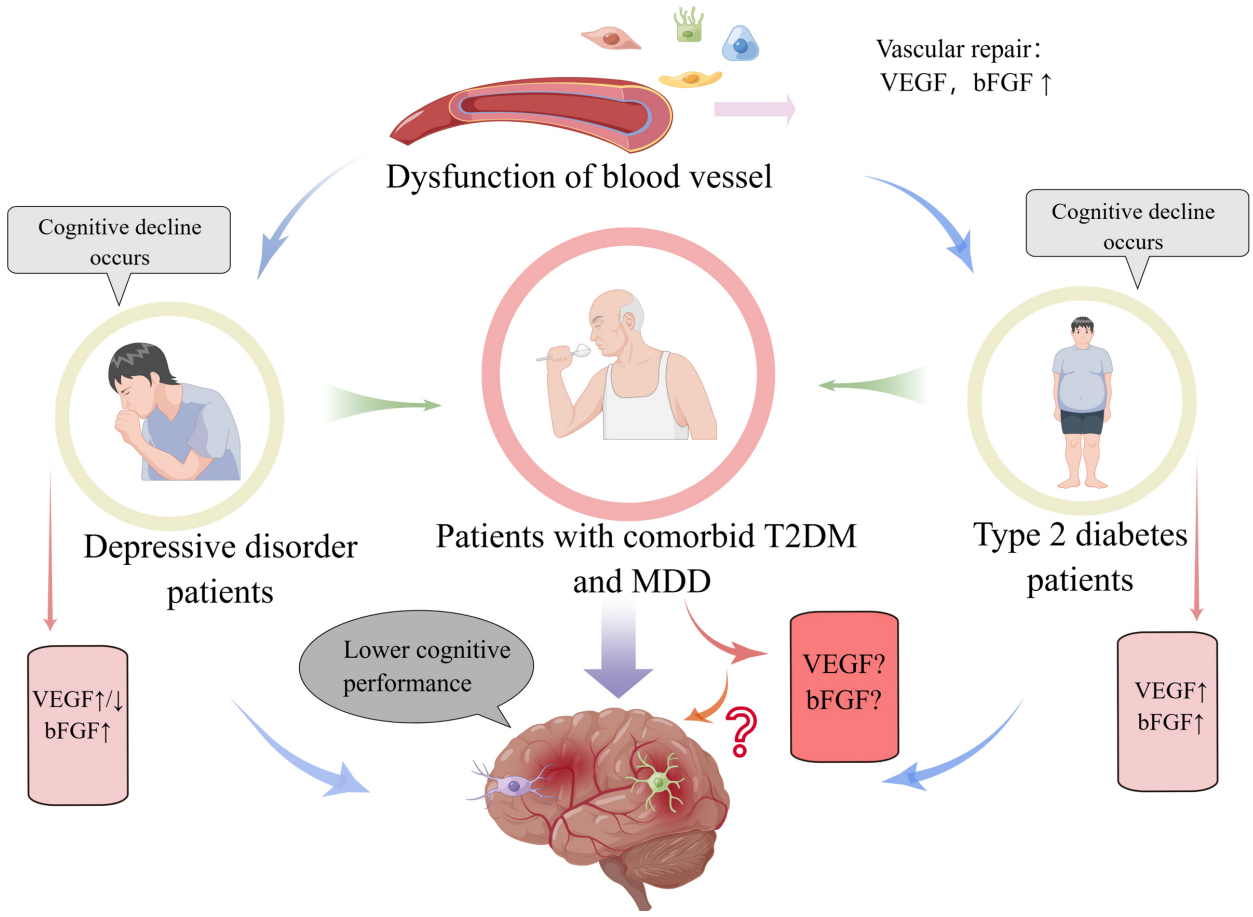


Fig. 1. Association of VEGF, bFGF with comorbidity of T2DM and MDD and cognitive decline. VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; T2DM, type 2 diabetes mellitus; MDD, major depressive disorder. Figure created with https://www.figdraw.com.

cretion of bFGF promotes the proliferation of fibroblasts and vascular endothelial cells [26]. Furthermore, VEGF plays a role in promoting neurogenesis, neuronal protection, and the regulation of synaptic plasticity [27,28]. Similarly, bFGF exerts neurotrophic and neuroprotective effects in the nervous system and is involved in the regulation of neuronal survival, synaptogenesis, neurite outgrowth, and neurogenesis [29,30]. Therefore, dysregulation of vascular growth factors may affect the integrity and function of the neurovascular unit, thereby influencing the glymphatic-brain clearance system and ultimately contributing to cognitive impairment.

The pathogenesis of comorbidity of T2DM and MDD and its cognitive decline is still unclear. Although vascular dysfunction is closely associated with the onset and subsequent cognitive decline of both isolated MDD and isolated T2DM, these two conditions rarely exist in isolation in clinical practice. In fact, T2DM and MDD frequently co-occur [31]. Currently, the prevalence of MDD in T2DM patients is still on the rise [32,33]. However, most existing studies have investigated vascular mechanisms—including endothelial dysfunction and alterations in vascular growth factors such as VEGF and bFGF—exclusively within single-disease models. Both VEGF and bFGF are essential for the neurovascular unit and the glymphatic-brain clearance system in the brain, and each has been independently linked to MDD and T2DM. Nevertheless, few studies have systematically examined their roles in the comorbid context. The critical question remains whether the concurrent presence of T2DM and MDD produces a distinct or aggravated profile of vascular endothelial dysfunction, and whether this vascular pathology specifically drives the accelerated and lower cognitive performance observed in patients with TD. Among elderly individuals with T2DM, those with comorbid depression exhibit an over 2.5-fold higher risk of dementia [34]. It is imperative to determine whether elevated levels of VEGF and bFGF—beyond their associations with MDD or T2DM alone—serve as specific biomarkers or mechanistic contributors to cognitive decline in TD. To address this research gap, the present study aims to provide preliminary evidence for a shared vascular pathway and a vascular-glymphatic mechanistic pathway that are altered under comorbid conditions and underlie cognitive decline, thereby establishing a theoretical basis for future interventions targeting endothelial protection and glymphatic enhancement to prevent or delay cognitive decline in this high-risk population. As shown in Fig. 1.

Initially, we conducted a cross-sectional study to assess serum VEGF and bFGF levels and their associations with cognitive function in patients with comorbid T2DM and MDD (TD). Subsequently, we performed receiver operating characteristic (ROC) analysis to evaluate diagnostic performance and used multivariable logistic regression to examine independent associations with TD status after adjusting for confounders. Our findings suggest that VEGF and bFGF are elevated in TD and show weak inverse correlations with cognitive function, but their diagnostic performance is limited.

2. Materials and Methods

2.1 Participants

This cross-sectional study was performed in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines (see **Supplementary Materials**). All participants were recruited from the First Affiliated Hospital of Kunming Medical University (Kunming, Yunnan, China) and were divided into four groups: MDD group, T2DM group, TD group, and healthy control (HC) group. T2DM patients were recruited from the Department of Endocrinology, while TD and MDD patients were recruited from the Department of Psychiatry. Both inpatients and outpatients were included. Healthy controls were recruited from the local community and from hospital staff.

All participants were aged between 18 and 70 years. Diagnoses followed the International Classification of Diseases, Tenth Revision (ICD-10) criteria, as assessed by experienced clinicians. The inclusion criteria were as follows: participants in the MDD group met ICD-10 criteria for a depressive episode with a total score $\geq$17 on the 17-item Hamilton Depression Rating Scale (HAMD-17) and had no prior diagnosis of impaired glucose tolerance, impaired fasting glucose, or any form of diabetes mellitus [35,36,37]. Participants in the T2DM group met ICD-10 criteria for type 2 diabetes mellitus and had no lifetime diagnosis of major depressive disorder (HAMD-17 total score <17) [38]. Participants in the TD group met ICD-10 criteria for both a depressive episode and type 2 diabetes mellitus, with a HAMD-17 score $\geq$17. Healthy controls met neither ICD-10 criteria for a depressive episode nor for type 2 diabetes mellitus. Exclusion criteria were strictly applied to ensure a homogeneous study population. Participants were excluded if they met any of the following conditions: previous diagnosis of mental retardation, organic mental disorders, schizophrenia, bipolar disorder, obsessive-compulsive disorder, or any other mental disorders; presence of major organic brain diseases or significant systemic diseases, including but not limited to cerebral hemorrhage, cerebral infarction, Parkinson's disease, coronary artery disease, tumors, hypothyroidism, autoimmune diseases, or other major medical conditions; prior history of psychoactive substance abuse or dependence; or inability to effectively cooperate and complete all study procedures.

2.2 Measures

Participants' demographic data, including basic characteristics (age and gender), educational attainment in years, illness duration, and body size indicators: height, weight, BMI, waist circumference, hip circumference, and the waist-to-hip ratio (WHR), were recorded using a stan-

dardized clinical data collection form. The Hamilton Depression Rating Scale (17-item version, HAMD-17) and Hamilton Anxiety Rating Scale (HAMA), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were used to assess the participants' levels of depression, anxiety and cognitive function [39]. The RBANS assesses five cognitive function indicators, including immediate memory, delayed memory, attention, language, and visuospatial, each of which was statistically analyzed by converting raw scores of included items into standardized scores using age-stratified normative tables, and these five index scores were combined to compute the RBANS total score. All RBANS scores were treated as continuous variables in statistical analyses [40]. Fasting venous blood samples were collected from each participant after an overnight fast of at least 8 hours. Glycated hemoglobin (HbA1c) was tested centrally by the Clinical Laboratory Department of the First Affiliated Hospital of Kunming Medical University. All blood samples are submitted for testing within 2 hours of collection. An aliquot of 5 mL of whole blood collected in additive-free tubes was centrifuged at 3000 rpm for 15 minutes. After collection, the serum supernatant was promptly cryopreserved at –80 ℃ pending subsequent assay. Before measurement, frozen serum samples were thawed at room temperature and used for enzyme-linked immunosorbent assay (ELISA). Serum levels of VEGF and bFGF were measured using commercial ELISA kits (YJ044236 for VEGF, YJ055963 for bFGF; Elabscience Biotechnology, Wuhan, Hubei, China). All procedures were performed strictly according to the manufacturers' instructions. Each sample was measured in duplicate, and the mean concentration was used for analysis. For the VEGF kit, the detection range was 31.25–2000 pg/mL, the sensitivity was 18.75 pg/mL, and the mean recovery rate was 98%. For the bFGF kit, the detection range was 31.25–2000 pg/mL, the sensitivity was 18.75 pg/mL, and the mean recovery rate was 100%. Both intra-assay and inter-assay coefficients of variation were below 10%, demonstrating satisfactory assay reproducibility and consistency.

2.3 Statistical Analysis

All analyses were conducted in SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA). Data visualisation was generated with GraphPad Prism, Version 10.4.1 (GraphPad Software, Boston, MA, USA). Continuous variables were first tested for normality using the Shapiro-Wilk test and for homogeneity of variances using Levene's test. Variables that followed a normal distribution and had homogeneous variances were expressed as mean ± standard deviation (Mean ± SD). Comparisons among multiple groups were performed using one-way analysis of variance (ANOVA), followed by LSD tests for post hoc pairwise comparisons. Variables that did not follow a normal distribution or had unequal variances were expressed as [Median (P25, P75)], and comparisons among multiple groups were carried out using the Kruskal-Wallis test ($p < 0.05$ considered statistically significant), followed by Bonferroni-corrected post hoc pairwise comparisons to control the false positive rate. Categorical data were summarized as frequencies (proportions), and intergroup comparisons were performed using the chi-square test. ROC curves were plotted to compare the diagnostic efficacy of different serological indicators. After adjusting for relevant confounding variables, partial correlation analysis was conducted to examine the relationships between vascular factors and cognitive function. Pearson correlation were used to evaluate the collinearity between independent variables. Multicollinearity was considered absent when absolute correlation coefficients were less than 0.7 and variance inflation factor (VIF) values were below 5. Binary logistic regression was conducted using diagnostic grouping as the dependent variable (TD group = 1, HC = 0), while each growth factor was separately incorporated into the corresponding model as the primary independent variable to independently evaluate its predictive effect. Each potential influencing factor was individually entered into univariate logistic regression analysis first, and variables with $p < 0.1$ were subsequently included in a multivariate logistic regression model constructed using the enter method. Age, gender and waist circumference were forced into all regression models as confounding factors.

2.4 Consistency and Quality Control

We implemented strict quality control measures to ensure uniformity and standardization across all research evaluation procedures. Standardized inclusion/exclusion criteria and procedures were applied uniformly across all participants. All assessments and laboratory tests were performed by trained professionals following fixed protocols. Raw data were double-checked and independently entered by two researchers. Given the cross-sectional design and small sample size, all findings are presented as exploratory associations, not causal evidence.

3. Results

Of the initially recruited 206 participants, including 49 healthy controls, 50 patients with MDD, 53 patients with T2DM, and 54 patients with TD, 37 individuals were excluded for the following reasons: 16 did not meet the inclusion criteria, 10 refused to participate and 11 failed to complete all scale assessments and blood sample collection. Consequently, the final study cohort comprised 32 HC patients, 46 MDD patients, 49 T2DM patients, and 42 TD patients. (see Fig. 2 for details).

The demographic data of the subjects are presented in Table 1. The TD group had a significantly higher mean age relative to the other three groups. Males were overrepresented in the T2DM group, whereas females were overrepresented in the remaining three groups. The TD, HC, and MDD groups demonstrated lower height values than

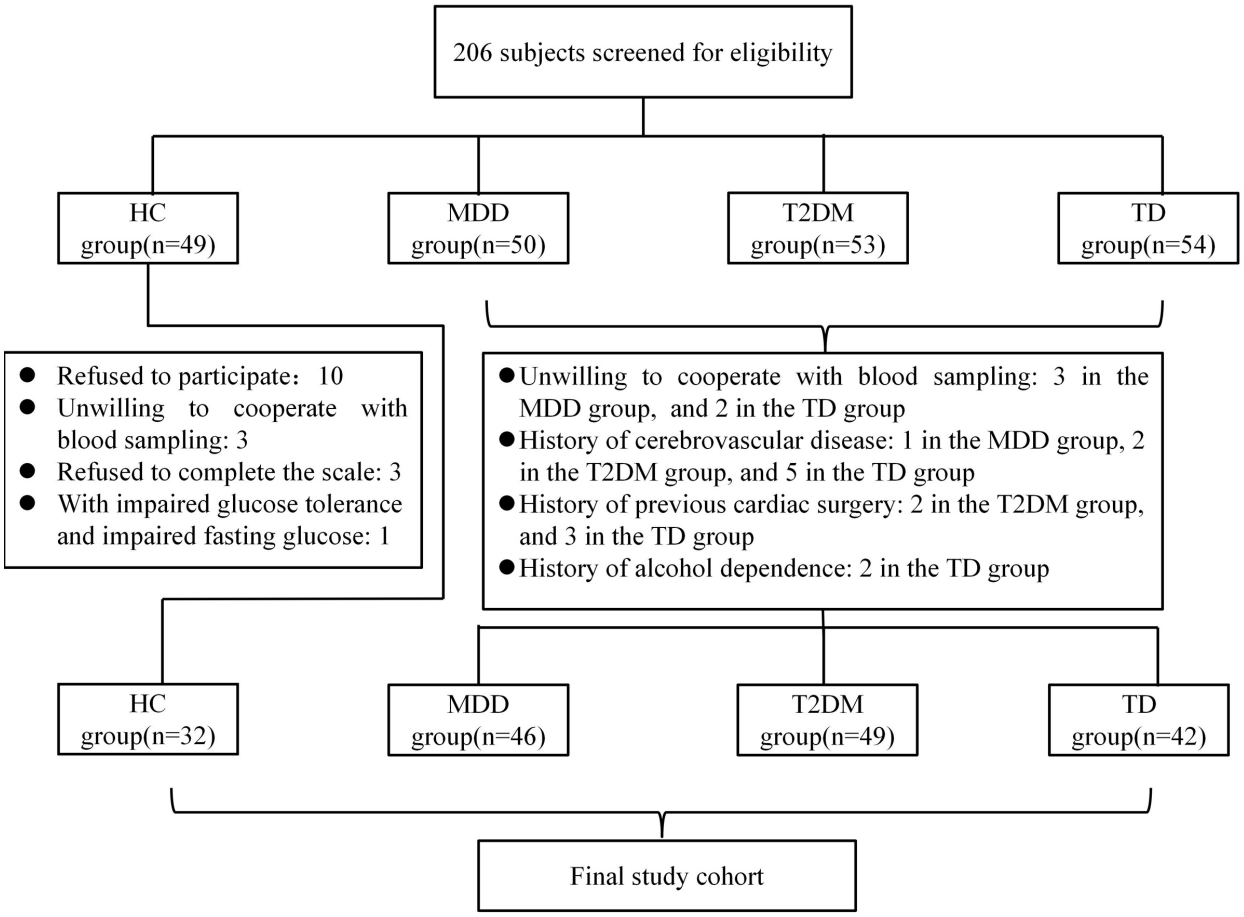


Fig. 2. Participant flow diagram. TD, patients with comorbid T2DM and MDD; HC, healthy control.

the T2DM group. Both the TD and MDD groups showed significantly lower weight compared to the T2DM group. Waist circumference was greater in the T2DM group than in the HC and MDD groups. Hip circumference measurements in the TD, MDD, and HC groups were lower relative to the T2DM group. A larger waist-hip ratio was observed in the TD group compared to the HC and MDD groups; similarly, the T2DM group had a larger waist-hip ratio than the HC group. The HbA1c level of the TD group was higher than that of the HC group and the MDD group (all $p < 0.05$). No significant differences were observed among the four groups regarding body mass index and years of education. No significant differences in disease duration were found across the three patient groups (MDD, T2DM and TD).

As shown in Table 2. Significant intergroup differences were found across the four groups for RBANS total score, immediate memory, delayed memory, attention, language, and visuospatial measures ($p < 0.05$). Compared with HCs, patients with MDD exhibited significantly lower total RBANS scores and scores across all RBANS domains. Relative to HCs, T2DM patients showed significantly lower scores in delayed memory, attention, language and visuospatial domains. The TD group had lower total RBANS scores and scores across all RBANS domains compared with HCs and patients with T2DM. Compared with the MDD group, the TD group demonstrated significantly poorer visuospatial performance. HAMD and HAMA scores also differed significantly across groups ($p < 0.05$), with the TD and MDD groups showing higher values than the HC and T2DM groups.

Serum VEGF was elevated in the TD and T2DM groups versus HC ($p < 0.05$). Serum bFGF was higher in TD than in HC ($p < 0.01$) and MDD ($p < 0.05$). As shown in Table 3.

The performance of serum VEGF and bFGF as predictive biomarkers in the TD group was evaluated by constructing ROC curves compared with the HC group. For the diagnosis of TD, serum VEGF yielded an area under the curve (AUC) of 0.66 (cut-off: 159.74 pg/mL, sensitivity: 0.88, specificity: 0.41, $p = 0.022$). Serum bFGF achieved an AUC of 0.718 (cut-off: 209.23 pg/mL, sensitivity: 0.381, specificity: 1, $p = 0.001$). As shown in Figs. 3,4.

After age and gender were used as control variables, various cognitive functions and serum VEGF and bFGF were included in the correlation analysis. The significance

Table 1. Participants' characteristics at baseline [Mean ± SD, Median (P25, P75)].

Variable	HC (n = 32)	MDD (n = 46)	T2DM (n = 49)	TD (n = 42)
Age (years)[c]	47.00 (40.50, 54.00)	48.50 (39.75, 58.00)	52.00 (43.00, 57.50)	59.00 (51.00, 65.25)[2*** 3*** 4*]
Gender (male/female)[b]	11/21	16/30	30/19[1* 5*]	18/24
Height (m)[a]	1.61 ± 0.13	1.62 ± 0.12	1.67 ± 0.11[1** 5**]	1.62 ± 0.11 [4**]
Weight (kg)[a]	63.47 ± 1.87	63.89 ± 1.52	67.86 ± 1.51[5*]	61.77 ± 1.72 [4**]
BMI (kg/m^2)[a]	24.18 ± 0.50	23.87 ± 0.48	24.26 ± 0.39	23.41 ± 0.53
Waist circumference (cm)[a]	85.00 ± 1.55	85.07 ± 1.56	91.43 ± 1.29[1** 5**]	88.83 ± 1.43
Hip circumference (cm)[a]	95.34 ± 1.08	92.54 ± 1.08	99.06 ± 1.11 [1*5***]	92.96 ± 1.13[4***]
waist-hip ratio[c]	0.88 (0.83, 0.92)	0.91 (0.85, 0.95)	0.92 (0.88, 0.97)[1*]	0.95 (0.92, 0.97)[2*** 3**]
Years of education (years) [c]	9.00 (6.00, 12.00)	9.00 (6.00, 15.00)	12.00 (9.00, 15.00)	12.00 (6.00, 12.75)
Duration of disease (years)[c]		2.00 (1.00, 4.00)	3.00 (1.00, 8.00)	3.00 (1.00, 7.50)
HbA1c (%)[c]	5.70 (5.40, 5.80)	5.70 (5.40, 5.90)	9.10 (7.05, 11.00)[1***5***]	6.40 (5.98, 7.58)[2*** 3***4**]

Statistical methods applied: [a] one-way ANOVA (data presented as mean ± SD), [b] chi-square test (data presented as frequency), [c] Kruskal-Wallis test (non-parametric, data shown as median with 25th-75th percentiles [M (P25, P75)]; **Group comparisons:** [1] HC vs. T2DM; [2] HC vs. TD; [3] MDD vs. TD; [4] T2DM vs. TD; [5] MDD vs. T2DM. *p*-values: *<0.05, **<0.01, ***<0.001. ANOVA, analysis of variance; SD, standard deviation.

Table 2. Comparison of cognitive function, HAMD and HAMA scores [Median (P25, P75)].

Variable	HC (n = 32)	MDD (n = 46)	T2DM (n = 49)	TD (n = 42)
Total RBANS [c]	479.00 (460.25, 518.25)	438.00 (370.00, 467.50)[6***]	465.00 (431.50, 498.50)[5*]	409.50 (360.75, 433.00)[2***4***]
Immediate memory [c]	81.00 (69.00, 87.00)	65.00 (53.00, 78.75)[6**]	81.00 (73.00, 87.00)[5***]	61.00 (49.00, 70.00)[2***4***]
Delayed memory [c]	98.00 (90.50, 107.00)	81.50 (74.00, 97.25) [6***]	94.00 (82.00, 101.00) [1*5*]	87.00 (64.00, 97.25) [2*** 4*]
Attention [c]	103.00 (100.00, 112.00)	97.00 (85.00, 106.00)[6***]	97.00 (91.00, 106.00)[1**]	89.50 (79.00, 100.00)[2***4**]
Language [c]	94.00 (88.25, 100.00)	87.00 (73.75, 94.00) [6***]	91.00 (83.50, 95.00)[1*]	86.00 (78.75, 92.00) [2***4*]
Visuospatial [c]	109.00 (97.50, 116.00)	92.00 (87.00, 103.75) [6**]	100.00 (88.00, 110.50) [1*]	85.50 (72.00, 96.00) [2***3*4**]
HAMD [c]	3.00 (2.00, 4.00)	25.00 (23.00, 28.25)[6***]	2.00 (1.00, 3.50)[5***]	25.00 (21.75, 27.00)[2***4***]
HAMA [c]	3.00 (2.00, 4.00)	18.50 (14.00, 23.00)[6***]	1.00 (0.50, 3.00)[5***]	18.00 (15.50, 22.25)[2***4***]

Statistical methods applied: [c] Kruskal-Wallis test (non-parametric, [M (P25, P75)]; **Group comparisons:** [1] HC vs. T2DM; [2] HC vs. TD; [3] MDD vs. TD; [4] T2DM vs. TD; [5] MDD vs. T2DM; [6] HC vs. MDD. *p*-values: *<0.05, **<0.01, ***<0.001. HAMD, hamilton depression rating scale; HAMA, hamilton anxiety rating scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 3. Comparison of serum VEGF and bFGF levels [Median (P25, P75)].

Variable	HC (n = 32)	MDD (n = 46)	T2DM (n = 49)	TD (n = 42)
VEGF[c]	204.70 (152.06, 427.93)	217.09 (149.32, 819.14)	232.32 (178.64, 961.12) [1*]	214.16 (172.03, 1212.47) [2*]
bFGF[c]	82.73 (68.21, 101.97)	85.18 (65.94, 186.29)	94.28 (70.33, 294.51) [1*]	98.16 (83.54, 358.75) [2**3*]

Statistical methods applied: [c] Kruskal-Wallis test (non-parametric, data shown as [M (P25, P75)]; **Group comparisons:** [1] HC vs. T2DM; [2] HC vs. TD; [3] MDD vs. TD. *p*-values: *<0.05, **<0.01.

level was adjusted to 0.00417 using the Bonferroni correction for multiple comparisons. After correction, VEGF was significantly negatively correlated with RBANS total scores, delayed memory, language and visuospatial scores (all $p < 0.00417$), whereas no significant correlations were observed between VEGF and immediate memory or attention scores. Additionally, bFGF showed no significant correlation with any dimension of RBANS (all $p > 0.00417$). As shown in Table 4.

When further adjusting for HbA1c, VEGF was significantly negatively correlated with RBANS total scores ($r = –0.239$, $p = 0.002$), delayed memory ($r = –0.251$, $p = 0.001$), language ($r = –0.320$, $p < 0.001$) and visuospatial scores ($r = –0.223$, $p = 0.004$), and no significant correlation was found between bFGF and any RBANS subscore after correction (see **Supplementary Materials**).

The Pearson correlation showed that the absolute values of the correlation coefficients between all independent variables (VEGF, bFGF, age, waist circumference, and HbA1c) were less than 0.7. The VIF values ranged from 1.069 to 1.809, well below 5, indicating that there is no significant multicollinearity issue in the model (see **Supplementary Materials**). Each potential influencing factor was individually entered into univariate logistic regression analysis, and variables with $p < 0.1$ were subsequently included in a multivariate logistic regression model constructed using the enter method. Binary logistic regression was conducted using diagnostic grouping as the dependent variable

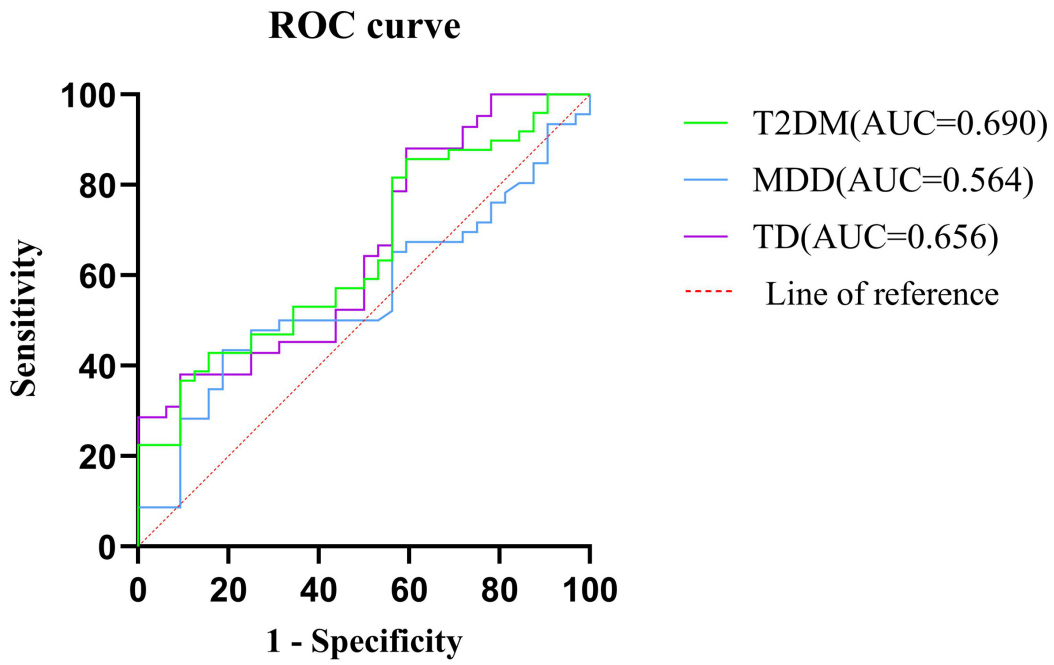


Fig. 3. ROC curve of serum VEGF. ROC, receiver operating characteristic; AUC, area under the curve.

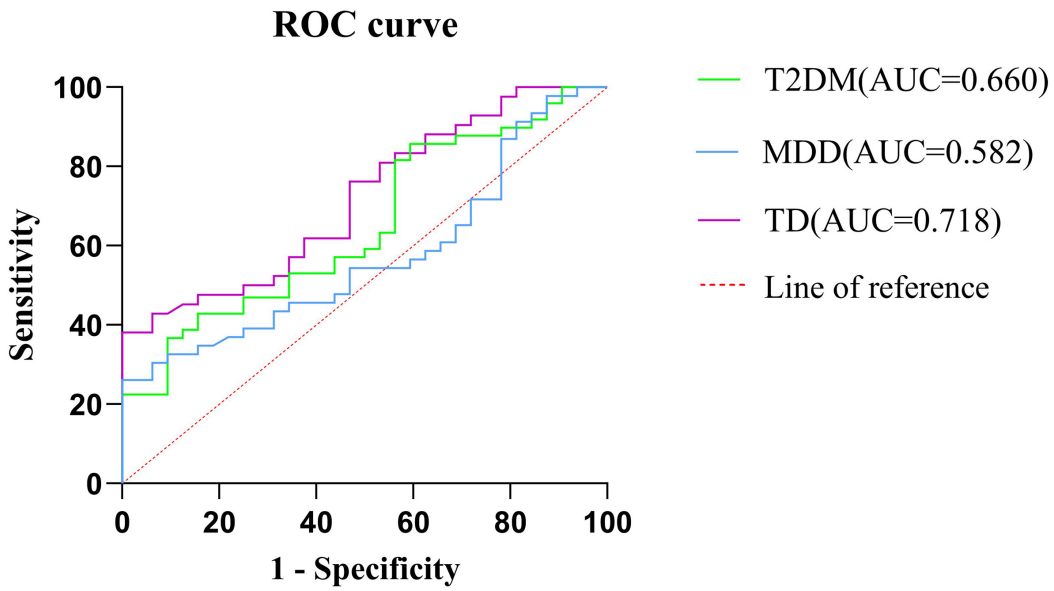


Fig. 4. ROC curve of serum bFGF.

Table 4. Correlation analysis between serum vascular growth factors and cognitive functions.

Variable	RBANS total scores	Immediate memory scores	Delayed memory scores	Attention scores	Language scores	Visuospatial scores
VEGF	**–0.241 (p = 0.002)**	–0.09 (p = 0.246)	**–0.256 (p = 0.001)**	–0.057 (p = 0.468)	**–0.326 (p < 0.001)**	**–0.234 (p = 0.002)**
bFGF	–0.062 (p = 0.428)	0.01 (p = 0.901)	–0.092 (p = 0.235)	–0.032 (p = 0.686)	–0.188 (p = 0.015)	0.028 (p = 0.723)

Notes: All of the above were analyzed using partial correlation analysis. Bold values indicate statistical significance. $p < 0.00417$ after Bonferroni correction for multiple comparisons.

(TD group = 1, HC = 0), while each growth factor was separately incorporated into the corresponding model as the primary independent variable. Covariates included age, gender and waist circumference.

As presented in Table 5, the results showed that serum levels of VEGF and bFGF were significantly positively correlated with TD. Increasing age was significant in both models (VEGF model: OR = 1.118, 95% CI: 1.052–1.189, $p < 0.001$; bFGF model: OR = 1.128, 95% CI: 1.051–1.211, $p = 0.001$) (see **Supplementary Materials**).

Table 5. Binary logistic regression analysis of serum VEGF and bFGF.

Variable	OR (95% CI)	*p*
VEGF	1.002 (1.000–1.003)	0.031
bFGF	1.016 (1.003–1.029)	0.017

Notes: Adjusted for age, gender and waist circumference.

To further evaluate the independent effects of VEGF and bFGF on TD, HbA1c was further included as a covariate in the regression analysis. The results showed that: the effects of both VEGF and bFGF were no longer statistically significant (VEGF: $p = 0.105$; bFGF: $p = 0.265$). In contrast, HbA1c itself showed a strong correlation with TD (VEGF model: OR = 10.637, 95% CI: 2.278–49.680, $p = 0.003$; bFGF model: OR = 10.299, 95% CI: 1.923–55.167, $p = 0.006$) (see **Supplementary Materials**).

4. Discussion

Current evidence has sufficiently demonstrated a correlation between elevated blood glucose levels and depressive symptoms [41]. It has also been suggested that patients with TD may have more pronounced depressive symptoms and a significantly increased risk of suicide [42]. This may be explained by the fact that poor glycemic control increases diabetes-related psychological distress, which in turn exacerbates depressive symptom severity, making depressive symptoms more difficult to manage when both disorders coexist [43,44]. In the present study, compared with the HC and T2DM groups, the TD and MDD groups showed significantly higher HAMD and HAMA scores. However, no significant difference was observed between the TD and MDD groups, indicating comparable levels of depression and anxiety severity. This comparability may be partly attributable to the use of glucose-lowering medications in the TD group, which could have alleviated some of the adverse emotional effects of hyperglycemia. As mentioned earlier, patients with MDD demonstrate progressive cognitive decline, potentially leading to dementia [5]. The risk of cognitive impairment in T2DM patients was more than double that in the HC group [45]. In our study, relative to the HC group, the MDD group exhibited significantly reduced scores across all RBANS domains, and the T2DM group likewise displayed lower cognitive performance, particularly in attention domains, aligning with prior reports. Patients with TD exhibit an increased risk of cognitive decline and dementia [46]. Moreover, their dementia risk exceeds the sum of the individual risks of T2DM and MDD alone, which is particularly evident in individuals under 65 years of age [47]. In our study, the TD group showed significantly lower cognitive performance than the HC group across all domains, including total score, immediate memory, delayed memory, attention, language, and visuospatial scores, which is consistent with the above findings. Further pairwise comparisons revealed that TD had lower visuospatial scores relative to MDD and performed significantly worse across all RBANS domains compared with T2DM patients.

Microvascular dysfunction may be one of the key factors linking MDD to cardiovascular disease [48,49]. Vascular dysfunction in patients with MDD promotes atherosclerosis, ultimately increasing the risk of cardiovascular disease [50]. T2DM will also lead to microvascular dysfunction due to hyperglycemia and glucose fluctuations, and can induce upregulation of pro-inflammatory mediators in vascular endothelial cells, leading to vascular endothelial dysfunction [20]. Studies have shown that TD patients with vascular complications are at an increased risk of cognitive dysfunction [51]. Alterations in VEGF levels have been associated with cognitive impairment, although the direction of this association may vary depending on the biological compartment, and study population [52]. During angiogenesis, VEGF and bFGF have been shown to act synergistically promoting vascular endothelial cell proliferation and blood vessel formation through distinct signaling pathways [53]. These growth factors can stimulate neurogenesis, leading to improved memory function [54,55]. Meanwhile, they exert neuroprotective effects by attenuating neuronal injury and apoptosis, which may contribute to the preservation of cognitive function under conditions of cerebral ischemia and hypoperfusion [56,57].

Patients with MDD exhibit higher peripheral VEGF levels than healthy controls, suggesting that VEGF may contribute to the pathogenesis and therapeutic response of MDD [58]. However, other studies report lower VEGF levels during MDD episodes, with no significant changes after antidepressant treatment, and levels remaining below those of healthy controls [59]. To explain the inconsistencies among these findings, some researchers have proposed that elevated VEGF levels may serve as a marker of self-repair in damaged hippocampal cells. Conversely, low VEGF levels may indicate insufficient capacity of the body to cope with the current disease state [60]. For T2DM, it has been observed that VEGF levels may already be elevated in prediabetic patients [61]. In addition, VEGF level was elevated in the blood of patients with T2DM nephropathy, with the highest levels in T2DM patients with complications such as

renal impairment and end-stage renal disease, and increased further with the progression of proteinuria, suggesting that VEGF may be an early marker of microvascular complications [62]. A recent study has similarly demonstrated that the Chinese herbal compound Jiaotai Wan may exert therapeutic effects in both diabetes and MDD, potentially through key targets such as VEGF-A [63]. In this study, VEGF levels in both T2DM and TD groups were significantly higher compared to the HCs group, which was consistent with the findings of previous studies.

A previous animal study showed that high-frequency repetitive transcranial magnetic stimulation ameliorated depressive-like behaviors in rats subjected to chronic unpredictable mild stress, accompanied by increased astrocyte-related FGF2 expression, attenuation of neuronal apoptosis, and activation of the FGF2/FGFR1/p-ERK signaling pathway. These findings suggest that the FGF2-associated signaling pathway may contribute to the antidepressant-like effects of rTMS in rodents [64]. In T2DM, bFGF exerts endothelial protection against endothelial damage caused by hyperglycemia and delays excessive chronic inflammation induced by diabetes during the early stages of T2DM [65]. Consistent with previous reports, bFGF levels in both TD and T2DM groups were significantly higher compared to the HC group in the present study. This study found no significant difference in bFGF level between the MDD and the HC groups, which may be due to variability in sample storage duration among MDD participants and potential proteolytic degradation by enzymes such as plasmin. In subsequent studies, the access time of serum samples in each group will be further tightly controlled to further clarify the bFGF levels in MDD patients.

After controlling for age and gender, correlation analyses in the full study cohort showed that serum VEGF levels were significantly negatively correlated with RBANS total score, delayed memory, language, and visuospatial scores, but showed no significant correlation with immediate memory or attention. This pattern suggests that VEGF may selectively affect specific cognitive domains, particularly delayed memory ($r = –0.256$), language ($r = –0.326$), and visuospatial function ($r = –0.234$). The strongest effect was observed in the language domain, potentially reflecting that language function is more sensitive to vascular pathology. HbA1c is a core feature of T2DM. The hyperglycemic microenvironment can alter the expression of VEGF and bFGF, impairing cognitive function through mechanisms such as oxidative stress, accumulation of advanced glycation end products (AGEs), and microvascular damage. To elucidate the cognitive effects of growth factors independent of glycemic control, further adjustments for HbA1c were performed, and the negative correlations between VEGF and the aforementioned cognitive domains remained statistically significant. This finding is highly suggestive: the association between VEGF and cognition is not entirely mediated by blood glucose levels, but may involve a neurovascular pathway independent of hyperglycemia. Potential mechanisms include direct effects of VEGF on blood-brain barrier permeability, neurovascular coupling efficiency, or glymphatic clearance function [23,66]. However, the absolute values of these correlation coefficients ranged only from 0.22 to 0.32, indicating weak to moderate correlations with small effect sizes. Therefore, despite statistical significance, the clinical implications are limited, and these findings should not be overinterpreted as strong causal evidence. In all adjusted models, bFGF showed no significant correlation with any RBANS domain scores ($p > 0.00417$). It exhibited no independent association with cognitive function in this clinical sample, which may be attributable to disease stage, the inability of peripheral blood levels to reflect central nervous system effects, or limited sample size. The negative correlation between VEGF and cognitive performance, interpreted via the glymphatic-neurovascular framework, suggests that therapeutic strategies targeting glymphatic enhancement may be effective. Future interventional studies should examine whether such “glymphatic-friendly” approaches can slow cognitive decline in TD patients.

After age, gender and waist circumference were used as control variables, the results of binary logistic regression showed that serum levels of VEGF and bFGF were significantly positively correlated with TD. For each 1 pg/mL increase in VEGF, the odds of TD disease increased by 0.2% (OR = 1.002, 95% CI 1.000–1.003, $p = 0.031$), and for each 1 pg/mL increase in bFGF, the odds of TD disease increased by 1.6% (OR = 1.016, 95% CI 1.003–1.029, $p = 0.017$). However, after further adjusting for HbA1c, both associations became non-significant, while HbA1c itself showed a strong association with TD ($OR \approx 10.6$, $p < 0.01$). This phenomenon may occur in studies with small sample sizes and strong grouping variables. It suggests that HbA1c, a powerful biomarker of diabetic status, explains most of the variance previously attributed to VEGF and bFGF. Rather, elevated levels of these growth factors may be a consequence of poor glycemic control rather than independent pathological driving factors. Larger sample cohorts and continuous blood glucose monitoring data are required in future studies to verify the independent effects of VEGF and bFGF.

In the present study, ROC analysis of serum VEGF and bFGF levels between the HC group and the TD yielded AUC values of 0.66 and 0.718, respectively, suggesting low to moderate diagnostic efficacy. Specifically, at an optimal cutoff value of 159.74 pg/mL, VEGF exhibited a high sensitivity of 0.88 but a low specificity of 0.41. This high-sensitivity-low-specificity profile suggests that VEGF may hold some potential as a screening tool for identifying TD patients; however, the extremely low specificity implies a substantial number of false-positive results, rendering it unsuitable as a confirmatory diagnostic biomarker. For bFGF, at a cutoff value of 209.23 pg/mL, the specificity reached 1.0, whereas the sensitivity was only 0.381. This pattern

indicates that elevated bFGF levels are highly specific to TD, but the markedly low sensitivity means that a large proportion of TD patients would not be identified by this indicator, thus limiting its clinical applicability. Consequently, neither biomarker can serve as an independent diagnostic biomarker for TD; rather, they may be better suited as auxiliary components in a multi-marker combined diagnostic model.

Limitations

Several limitations should be considered when interpreting the findings of this study.

The cross-sectional design precludes any causal inferences regarding the relationships between VEGF/bFGF and cognitive decline or comorbid status. We are unable to determine temporal sequences, distinguish between "cause" and "accompanying phenomenon", or assess long-term dynamic changes. Therefore, all findings should not be interpreted as causal evidence, and mechanistic hypotheses need to be validated in longitudinal or interventional studies. The relatively small sample size in each group may have limited statistical power, particularly for detecting associations with small effect sizes (e.g., the correlation between bFGF and cognition, or the weak effect of VEGF after adjusting for glucose). Consequently, there is a risk of false-negative findings (Type II error), meaning that some true but weak associations may have been missed. Serum levels of VEGF and bFGF may not directly reflect their concentrations or activities within the central nervous system (CNS). Peripheral blood levels are influenced by systemic factors such as inflammation, metabolic status, and medication use, and may not accurately represent CNS-specific processes involving the neurovascular unit or glymphatic system. Future studies measuring cerebrospinal fluid biomarkers or employing neuroimaging techniques (e.g., DTI-ALPS) are needed to directly assess CNS involvement. Some patients with depression or T2DM were receiving antidepressant or glucose-lowering medications. The type, dosage, and duration of these medications may independently influence serum VEGF and bFGF levels as well as cognitive function. However, due to the small sample size, high heterogeneity in medication regimens (involving various combination therapies), and incomplete medication records lacking precise information on medication start/stop dates and adherence, we were unable to perform detailed statistical control or stratified analyses of these drug-related factors. Future studies could incorporate a medication washout period or enroll medication-naïve patients to more accurately assess the effects of the diseases themselves, rather than medications, on vascular growth factors and cognition. Differences were observed across the four groups in variables such as age, gender, weight, height, hip circumference, waist circumference, and waist-to-hip ratio. Although core confounders including age, sex, and waist circumference were adjusted for in the analyses, the presence of widespread baseline differences implies that residual confounding may still affect the results. Furthermore, in any observational study, the possibility of unmeasured or unknown confounders always exists. For example, lifestyle factors (diet, physical activity, smoking, alcohol consumption), socioeconomic status, educational level, and genetic background may simultaneously influence T2DM, MDD, VEGF levels, and cognitive function; however, these variables were not included in the present study.

Given these limitations, the findings of this study should be viewed as exploratory rather than conclusive. The main observations would benefit from further validation in larger, prospective, multicenter studies to help clarify the underlying mechanisms. We will strictly balance baseline characteristics across all groups during subject enrollment to minimize inherent group differences in advance or adopt more rigorous statistical methods such as propensity score matching to further eliminate confounding bias and enhance the reliability of causal inference. It may be valuable to explore the temporal sequence and potential causal relationship between VEGF/bFGF and cognitive decline through large-sample longitudinal studies. Interventional trials could be considered to assess whether glucose-lowering, antidepressant, or vascular growth factor-targeted therapies might offer cognitive protective effects. It would also be worthwhile to examine the feasibility of multi-marker combinatorial prediction models to enhance early identification. Ultimately, efforts may be directed toward the development of clinical screening tools and multi-target intervention strategies, which could contribute to the early prevention and more precise management of cognitive decline in patients with TD.

5. Conclusions

In conclusion, this study provides preliminary evidence suggesting a shared vascular pathway, as well as a vascular-glymphatic mechanistic pathway that may be amplified in patients with the comorbidity of T2DM and MDD. Patients with TD exhibited significantly elevated serum levels of VEGF and bFGF, along with significantly lower cognitive performance. Moreover, correlation analyses across the full study cohort showed that a negative correlation was observed between serum VEGF levels and RBANS total scores, delayed memory, language, and visuospatial scores, indicating that higher VEGF levels were associated with poorer cognitive performance. However, neither VEGF nor bFGF demonstrated sufficient independent diagnostic value, and their effect sizes in logistic regression were very small, indicating that neither marker alone can serve as a standalone biomarker for TD. Instead, they may function as auxiliary components within a multi-marker diagnostic model.

Critically, the concurrent presence of T2DM and MDD was associated with an aggravated profile of vascular endothelial dysregulation that appeared more pronounced

than that observed in either disorder alone. These findings are broadly consistent with the emerging neurobiological model that implicates glymphatic system impairment as a common pathway linking vascular pathology to cognitive decline. Nevertheless, given the cross-sectional design and relatively small sample size, all findings should be interpreted as exploratory associations rather than causal evidence. Independent validation in larger, prospective, longitudinal cohorts is essential before considering clinical applications of these growth factors as biomarkers or therapeutic targets for preventing or delaying cognitive decline in patients with TD, who face accelerated cognitive decline and a substantially increased risk of dementia.

Abbreviations

T2DM, Diabetes Mellitus, Type 2; MDD, major depressive disorder; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

DY: made contributions to the conception and design of the work, data acquisition, analysis, interpretation and wrote the manuscript. MY: made contributions to data acquisition, interpretation and revised the manuscript. LS: made contributions to the conception of the work, data acquisition, and revised the manuscript. NL: made contributions to conception of the work, data interpretation and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University, ethical approval number: (2022) Ethics L No. 138. Informed consent was obtained from all subjects who voluntarily participated in the research.

Acknowledgment

We thank all the patients who participated in the study.

Funding

This work was supported by Yunnan Province Xingdian Talent Support Plan (Grant NO.RL2024RLMY0007); The National Natural Science Foundation of China (Grant NO.82160164); The Science and Technology Program Project of the Yunnan Provincial Department of Science and Technology (Grant NO.202301AY070001-290); The Funding of the Young Talents Project of the Support Plan for the Talents of Xing dian (Grant NO.RLQ820220008).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/AP48990.

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