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ORIGINAL STUDY

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Plasma VEGF-A, VEGFR-2, and Asprosin Levels in Poorly Controlled Type 2 Diabetes

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Abstract

Background: Poorly controlled type 2 diabetes is marked by endothelial dysfunction and disrupted glucose metabolism. VEGF-A and VEGFR-2 drive vascular repair, while asprosin contributes to insulin resistance.

Objectives: This study explored the association of these biomarkers in individuals with poorly controlled T2DM.

Methods: The study included 100 patients with type 2 diabetes mellitus (T2DM) and 60 age-matched healthy controls (45–65 years). Glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were measured using a Roche Cobas Integra 400 Plus analyzer. Serum levels of VEGF-A, VEGFR-2, and asprosin were quantified using ELISA.

Results: T2DM patients exhibited significantly elevated serum levels of VEGF-A, VEGFR-2, and asprosin compared with controls ($p < 0.001$). Asprosin showed significant correlations with both VEGF-A and VEGFR-2. Additionally, VEGF-A and asprosin were strongly associated with glucose levels, whereas no meaningful correlation was observed between these biomarkers and the overall duration of diabetes, BMI, and lipid profiles, except for a modest association observed between VEGF-A and duration of disease.

Conclusion: VEGF-A, VEGFR-2, and asprosin levels were elevated in T2DM patients, reflecting their roles in angiogenesis and metabolic dysregulation. Poor glycemic control further increased these markers, highlighting the importance of effective glucose management to mitigate related complications.

Keywords: VEGF-A, VEGFR-2, Asprosin, T2DM

1. Introduction

Type 2 diabetes mellitus (T2DM), the most prevalent type of diabetes worldwide, is a metabolic disease marked by insulin resistance or insufficient insulin secretion as a result of the pancreatic β-cells gradually declining [1]. A complex interaction of environmental and/or genetic factors leads to this syndrome [2]. Adipose tissue is an endocrine organ that produces adipokines in addition to being an insulating and energy-storing organ. The FBN1 gene encodes the recently discovered fat hormone asprosin, which is centrally orexigenic, crosses the blood-brain barrier, and stimulates the liver to release glucose into the bloodstream [3–6]. It also encourages the manufacture of insulin. Insulin resistance, obesity, and T2DM are all linked to elevated asprosin levels [5, 7]. Asprosin decrease significantly reduced insulin and glucose [4]. Treating diabetes and its complications may be benefited by therapeutically targeting asprosin. Since its discovery, a number of studies have investigated the relationships between asprosin and diabetes and insulin resistance in people. These studies have discovered that circulating asprosin levels were elevated in type 2 diabetes and positively linked with HOMA-IR [8–10].

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By binding to its primary receptor, OR4M1 (Olfactory Receptor Family 4 Subfamily M Member 1) in humans or its homolog Olfr734 in mice, asprosin directly stimulates target cells [11]. Binding to OR4M1 activates the G protein–cAMP–PKA pathway [12]. This activation enhances signaling in pathways associated with angiogenesis and cell proliferation, particularly in organs such as the placenta and vascular endothelium. Specifically, it upregulates VEGF-A, which subsequently binds to and phosphorylates VEGFR-2, leading to vascular alterations [12].

Vascular permeability factor (VPF), another name for VEGF, is a multifunctional growth factor essential for vascular endothelial cells [13, 14]. It plays a role in the cardiovascular system [15], central nervous system [16], carcinogenesis [18], and both physiological and pathological neovascularization [17]. VEGF-A, a member of the VEGF family, is a key regulator of the vascular system [19]. It interacts with specific receptors, including VEGFR-2 (KDR/Flk-1), VEGFR-1 (Flt-1), and VEGFR-3 (Flk-4), which belong to the receptor tyrosine kinase (RTK) subfamily [20]. These interactions drive lymphangiogenesis (mediated by VEGF-C and VEGF-D) and blood vessel proliferation (driven by VEGF-A, VEGF-B, VEGF-C, and VEGF-E) [21, 22].

The VEGF/VEGFR system is a major target for both anti-angiogenic therapy in cancer and pro-angiogenic therapy in neuronal degeneration and ischemic disorders [23]. VEGFR-2 is the primary receptor responsible for mediating VEGF-A–induced vascular permeability [24]. In many clinical conditions, such as wound healing, rheumatoid arthritis, diabetic retinopathy, Alzheimer's disease, small vessel disease, coronary heart disease, and cancer, the formation of new blood vessels depends on VEGF-A activation of VEGFR-2 [25].

2. Materials and methods

2.1. Study population

The average age of the 100 T2DM patients in this study was 55.18 ± 8.44 years, ranging from 45 to 65 years. Fifty males and fifty women were included. The control group consisted of 30 females and 30 men who were matched for age (mean 54.90 ± 8.98 years) and seemed to be in good health. Patients and controls were recruited in the Internal Medicine Unit of the Baquba Teaching Hospital in Diyala, Iraq, between January 2024 and July 2025.

2.2. Diagnostic and classification criteria

According to the American Diabetes Association (ADA) protocol [26], specialized experts diagnosed T2DM and selected poorly controlled hyperglycemic patients based on clinical characteristics, laboratory findings (HbA1c > 7%), fasting plasma glucose (FPG), and clinical history. The patients had a mean duration of diabetes of 7.5 ± 3.1 years. In addition, all patients were categorized according to BMI in accordance with WHO guidelines [27].

2.3. Sample collection

Following an 8–10 hour overnight fast, blood samples were drawn intravenously using disposable 5 mL syringes. 4 mL of blood was transferred to gel tubes for serum separation, and the first mL was transferred to EDTA tubes for HbA1c measurement. The serum was utilized right away to measure fasting plasma glucose, total cholesterol (TG), triglyceride (TG), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), and the rest was kept at -20°C for three months until VEGF-A, VEGFR-2, and asprosin analysis.

2.4. Laboratory analyses

VEGF-A, VEGFR-2, and asprosin concentrations were assessed using the enzyme-linked immunosorbent assay (ELISA) technique (MyBioSource, USA). The Cobas Integra 400 Plus autoanalyzer from Roche Diagnostics was used to measure fasting plasma glucose and HbA1c. Sex, age, marital status, length of disease, age at onset, treatment received, family history, and prior medical or surgical history were among the other demographic and clinical information gathered.

2.5. Exclusion criteria

Exclusion criteria encompass individuals with liver or renal disease, neurological disorders, T1DM, other autoimmune conditions like Hashimoto's thyroiditis, a history of infections, pregnant women, those on cortisol medication, and individuals with other chronic illnesses.

2.6. Statistical analysis

Statistical analysis was performed using SPSS software. Data normality was assessed using the Shapiro–Wilk test. Based on data distribution, the independent samples t-test and Spearman's correlation were applied. Chi-square tests were used to evaluate associations between variables and study groups.

3. Results

According to Table 1, the most common category among the patient group was overweight (n = 42,

Table 1. Frequency table for BMI categories in the study subjects.

Variable	Category	Patients (N = 100)	Control (N = 60)	P-Value
BMI categories	Normal (18.5–24.9)	13 (13%)	24 (40 %)	0.004*
	Overweight (25–29.9)	42 (42%)	21 (35%)	
	Obese Class I (30–34.9)	34 (34%)	8 (13.3%)	
	Obese Class II (35–39.9)	11 (11%)	7 (11.6%)	

42%). In addition, a considerable proportion of patients were classified as obese class I (n = 34, 34%). There was a statistically significant difference between patients and controls in the distribution of BMI categories (p = 0.004).

The mean values of TC, TG, LDL, and HDL in patients were 196.60 ± 48.39, 241.11 ± 108.94, 118.77 ± 38.87, and 39.27 ± 8.74, respectively, while the corresponding mean values in the control group were 164.71 ± 28.31, 121.86 ± 39.66, 107.63 ± 26.17, and 43.29 ± 7.53, respectively. There was a statistically significant difference between the two groups, with p-values of < 0.001, < 0.001, 0.037, and 0.001, respectively (Table 2).

The mean levels of VEGF-A, VEGFR-2, and asprosin were significantly higher in patients with T2DM compared to healthy controls (p < 0.001). Additionally, HbA1c and fasting blood glucose (FBG) levels were significantly elevated in patients versus controls (p < 0.001) (Table 3 and Fig. 1).

3.1. Correlation analysis of variables among T2DM patients

The statistical analysis revealed a significant positive correlation between VEGF-A and VEGFR-2 (r = 0.55, 95% CI [0.47, 0.71]; p < 0.001), indicating that their levels rise in tandem. Asprosin also showed a strong positive correlation with VEGF-A (r = 0.70, 95% CI [0.61, 0.80]; p < 0.001) and an even stronger correlation with VEGFR-2 (r = 0.82, 95% CI [0.82, 0.91]; p < 0.001), suggesting coordinated increases among these biomarkers (Fig. 2). HbA1c did not correlate substantially with the duration of T2DM, whereas VEGF-A showed a modest positive correlation (r = 0.19, p = 0.04). Serum Asprosin was positively associated with fasting blood glucose (FBG) (r = 0.22, p = 0.029). Additionally, VEGF-A levels correlated significantly with both FBG and disease duration (r = 0.21, p = 0.03) (Table 4).

Table 2. Mean values of the TC, TG, LDL, and HDL were compared between the patients and control groups.

Variables	group	Mean ± SD	SEM	P value
TC (Less than < 200 mg/dL)	Control	164.71 ± 28.31	3.41	< 0.001*
	patients	196.60 ± 48.39	4.63	
TG (<150 mg/dL)	Control	121.86 ± 39.66	4.77	< 0.001*
	patients	241.11 ± 108.94	10.43	
LDL (100–129 mg/dl)	Control	107.63 ± 26.17	0.91	0.037*
	patients	118.77 ± 38.87	0.84	
HDL more or equal to 40 mg/dl	Control	43.29 ± 7.53	3.15	0.0019*
	patients	39.27 ± 8.74	3.72	

*Significant using two-tailed independent samples t-test at 0.05 level, SEM = Standard error of the mean.

Table 3. Comparison of mean parameter values between T2DM patients and healthy controls.

Variables	Groups	Mean ± SD	P value
VEGF-A (pg/ml)	Control	172.02 ± 24.67	< 0.001
	Patients	754.83 ± 209.60	
VEGFR-2 (pg/ml)	Control	205.39 ± 29.16	< 0.001
	Patients	736.16 ± 156.56	
Asprosin (ng/ml)	Control	3.51 ± 0.43	< 0.001
	Patients	7.84 ± 2.2	
Glucose (mg/dl)	Control	104.71 ± 10.3	< 0.001
	Patients	265.4 ± 67.5	
HbA1c (%)	Control	5.31 ± 0.41	< 0.001
	patients	9.3.6 ± 2.00	

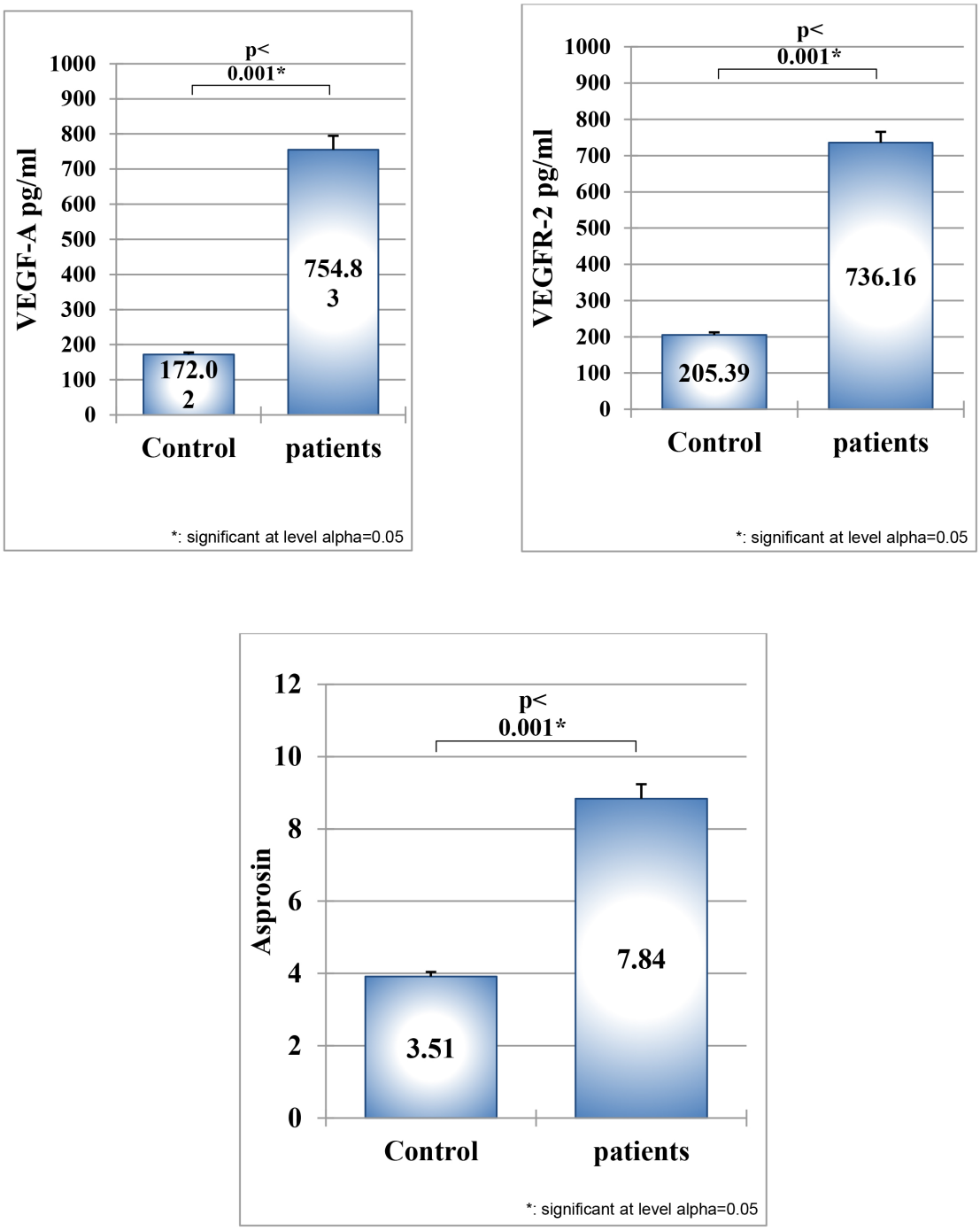

Fig. 1. Mean differences in VEGF-A, VEGFR-2, and asprosin levels between T2DM patients and healthy controls.

Asprosin, VEGF-A, and VEGFR-2 did not significantly correlate with BMI <25 kg/m2, BMI ≥25 kg/m2,TC, HDL, LDL and TG in patients individuals ($p > 0.05$), according to data in (Table 5).

The data presented in Table 6 demonstrate the ability of asprosin, VEGF-A, and VEGFR-2 to differentiate between patients with type 2 diabetes mellitus and control participants. The diagnostic accuracy of these biomarkers was indicated by high area under the curve (AUC) values obtained from ROC curve analysis. Asprosin, VEGF-A, and VEGFR-2 showed AUC values of 0.990, 0.975, and 0.993, respectively, all of which were statistically significant ($p < 0.0001$).

The sensitivity and specificity of these markers were calculated using specific cut-off values. VEGFR-2 demonstrated a sensitivity of 96.36% and a

Table 4. Correlations between serum biomarkers (VEGF-A, VEGFR-2, Asprosin) and primary diabetes indicators (FBG, HbA1c, disease duration) in T2DM patients.

Variables		Asprosin	VEGF-A	FBG	HbA1c	Disease Duration
VEGF-A (pg/ml)	r	0.70		0.21	0.12	0.19
	p	<0.001*		0.03*	0.22	0.04 *
VEGFR-2 (pg/ml)	r	0.82	0.55	0.14	0.07	0.14
	p	<0.001*	<0.001*	0.062	0.38	0.16
Asprosin (ng/ml)	r			0.22	0.06	0.15
	P			0.029*	0.32	0.11

*Correlation is significant at 0.05.

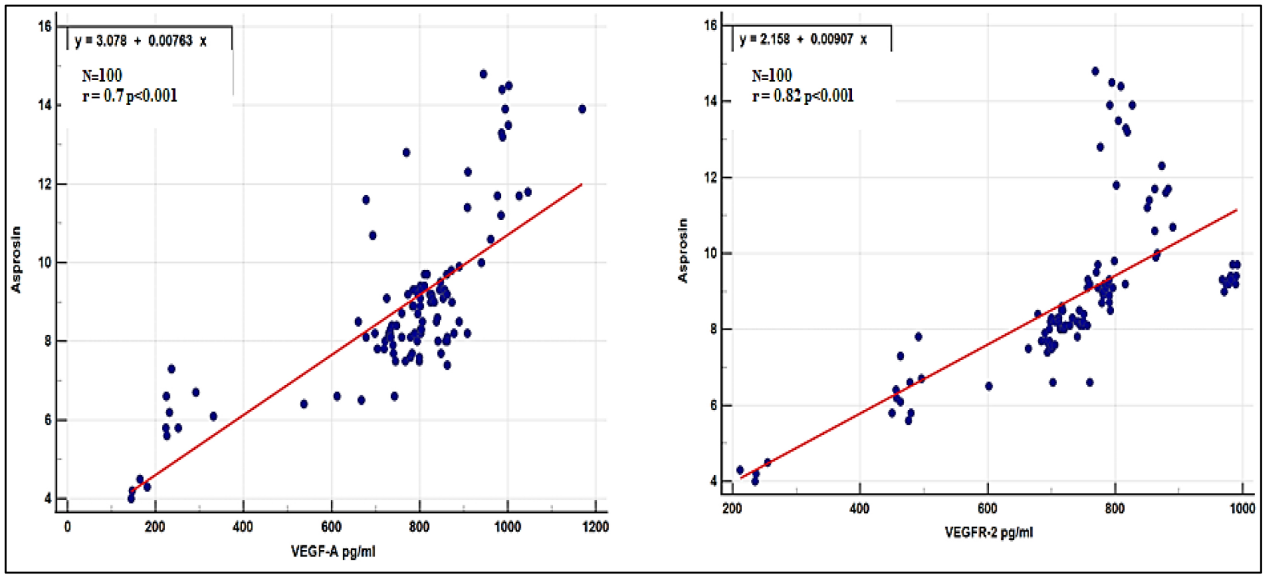

Fig. 2. Scatterplots with regression lines showing the relationships between asprosin and VEGF-A, and asprosin and VEGFR-2.

Table 5. Correlation between study markers and BMI, TC, HDL, LDL, and TG in patients' group.

		BMI <25 kg/m2	BMI ≥25 kg/m2	TC	HDL	LDL	TG
Asprosin ng /ml	r	0.26	0.06	–0.02	0.03	0.01	–0.01
	p	0.92	0.6	0.82	0.80	0.88	0.94
VEGFA pg/ml	r	0.08	–0.04	0.01	0.01	0.02	–0.04
	p	0.76	0.66	0.91	0.94	0.87	0.66
VEGFR-2 pg/ml	r	0.03	0.07	–0.13	0.11	–0.08	–0.07
	p	0.91	0.49	0.16	0.26	0.44	0.45

specificity of 100.00%, while asprosin showed a sensitivity of 96.36% and a specificity of 98.57%. VEGF-A exhibited a sensitivity of 96.36% and a specificity of 97.14% (Table 6).

4. Discussion

This study examined the relationship between BMI categories, lipid profiles, blood glucose, HbA1c, and serum levels of VEGF-A, VEGFR-2, and asprosin in individuals with T2DM. VEGF-A, a potent proangiogenic factor that stimulates endothelial cells and increases vascular permeability, is a key biological mediator of angiogenesis, a critical process in the development of diabetic microvascular complications [28]. The findings of this investigation align with another study that found that those with T2DM had higher levels of VEGF-A than people in good health [2]. A lipid molecule called diacylglycerol, which is produced by hyperglycemia, activates protein kinase C in vascular tissues, which in turn triggers VEGF-A signaling and leads to diabetic microvascular problems [29]. Furthermore, hypoxia, gender, smoking, hyperlipidaemia, inflammation, and stress axis activation all affect VEGF-A synthesis and secretion, with cellular hypoxia serving as the main physiological trigger for VEGF-A expression [30, 31]. Vascular endothelial cells have the initial VEGF-A binding sites on their surface, which is also where VEGFR2 is found [32], and VEGFR2 is the main receptor that

Table 6. ROC curve analysis criteria comparison among asprosin, VEGF-A, and VEGFR-2 as they classify patients from control subjects.

Variable	AUC	SE	95% CI	Cut off	Sensitivity	Specificity	P value
Asprosin	0.990	0.00528	0.962 to 0.999	>4.86	96.36	98.57	<0.0001*
VEGF-A	0.975	0.0126	0.940 to 0.993	>215	96.36	97.14	<0.0001*
VEGFR-2	0.993	0.00435	0.967 to 1.000	>276.7	96.36	100.00	<0.0001*

receives the VEGFA signal [33]. Moreover, the majority of VEGFA's physiological actions are mediated by VEGFR2 [32]. Any link between VEGF-A and the factors in the current study could be due to VEGFR2.

The current study's findings demonstrated that serum asprosin levels were significantly higher in poor control individuals with type 2 diabetes than in the control group. It may be brought on by insulin resistance or hyperglycemia and may be a risk factor for the emergence of more severe diabetes complications, such as diabetic retinopathy [24].The findings of this investigation are consistent with earlier investigations that have demonstrated a strong relationship between FBG and asprosin blood levels [34]. It is believed that asprosin is a highly sensitive biomarker of T2DM and obesity [35]. Zhang [36] states that high asprosin levels are a risk factor for type 2 diabetes and that abnormal asprosin release occurs in response to changes in blood glucose levels in patients with the illness.

The results of a previous study, which demonstrated that VEGF-A levels in T2DM patients were significantly higher than those in healthy individuals, were corroborated by the present study [2]. In contrast, a study by Ruszkowska [22] reported no statistically significant differences in VEGF-A and VEGFR-2 levels between the T2DM patient group and the control group. This discrepancy may be attributed to better glycemic control among the participants in that study.

Studies have shown that IR, adipose tissue mass, and BMI are negatively correlated with brown adipose tissue (BAT) activity [36]. The relationship between adipocytes and endothelial cells (EC) is essential for maintaining homeostasis [37]. Adipose tissue constantly remodels as it is confronted with energy status issues and secretes hormones, growth factors, and cytokines that control angiogenesis [38]. Angiogenesis is inhibited by the rise in hormone release from white adipose tissue (WAT) brought on by obesity and IR in diabetics. As a result, WAT has a substantially lower channel density than brown adipose tissue (BAT) [39]. According to studies, EC-produced VEGF can encourage fat browning [40, 41]. When WAT does not turn brown, more VEGFA and its receptor 2 are secreted, which controls angiogenesis, encourages fat browning, and influences lipid levels [42]. The present study's favorable correlation between asprosin and VEGF-A and its receptor 2 may be explained by the aforementioned relationships. One risk factor associated with the pathophysiology of type 2 diabetes mellitus is the circulating level of asprosin, which is considerably higher in patients with type 2 diabetes mellitus than in apparently healthy controls. Its effects appear to extend to metabolic regulation and angiogenesis.

The lack of association between BMI abnormalities and lipid profile parameters (TC, HDL, LDL, and TG) with asprosin, VEGF-A, and VEGFR-2 suggests that, within the context of this study, these parameters may not have a major influence on obesity-related mechanisms in type 2 diabetes mellitus. A study by Wang [43] found no association between BMI and serum asprosin levels in diabetic patients. Similarly, Sun [44] reported no significant correlation between VEGF-A and BMI in patients with T2DM. Finally, the findings of the present study are consistent with Wang [43] (2021), who also observed no relationship between serum asprosin concentrations and HbA1c, TC, TG, LDL, or HDL.

The AUC values, along with the high sensitivity and specificity, suggest that VEGF-A, VEGFR-2, and asprosin may serve as reliable diagnostic and prognostic biomarkers for assessing the degree of angiogenesis and metabolic dysfunction in T2DM.

5. Conclusion

T2DM patients exhibited elevated levels of VEGF-A, VEGFR-2, and asprosin, indicating their involvement in angiogenesis and metabolic dysregulation. Poor glycemic control was associated with increased expression of these biomarkers. Effective glucose management is therefore essential for modulating their levels and reducing diabetes-related complications.

Ethical clearance

The Research Committee of the Training and Human Development Center at the Diyala Health Department reviewed and approved the study protocol (Approval No. 4137). All participants were provided with a detailed explanation of the study objectives and procedures. Written informed

consent was obtained from each participant prior to enrollment in the study.

Competing interests

No known financial or non-financial conflicts of interest exist that could have impacted this research.

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