

Assessment of survivin mRNA expression level and its serum level in patients with diabetic retinopathy

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Abstract

Diabetic patients may suffer from diabetic retinopathy (DR) which may result in vision loss. Apoptosis is essential in vascular remodeling. Survivin inhibits endothelial cell apoptosis and enhances angiogenesis. Diabetic vasculopathy can increase survivin expression. Our aim is to measure the clinical significance of survivin mRNA expression and its serum level with DR as predictors for disease prognosis. Thirty patients with DR; thirty without DR and thirty healthy persons were included as controls (employees and attendants for checkup with normal HbA1c level). Ophthalmic examination, best corrected visual acuity assessment (BCVA), slit-lamp biomicroscopy, and fundoscopy, were done for all patients. DR was diagnosed by biomicroscopic fundus examination. Serum survivin level was estimated by enzyme linked immunosorbent assay (ELISA) technique and survivin messenger ribonucleic acid (mRNA) expression by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) as potential biomarkers of DR. Serum survivin was significantly increased in DR patients than those without DR ($p < 0.01$). Serum survivin and its mRNA expression correlated significantly and positively with HbA1c in DM patients ($r = 0.808$ and 0.618 , $p < 0.001$). Serum survivin has an AUC of 0.985 (95% CI: 0.955–1.000, $p < 0.001$) with a sensitivity of 96.67% and specificity of 93.33% at a cutoff value of >360 pg/mL. For survivin mRNA expression, the AUC was 0.907 (95% CI: 0.820–0.995, $p < 0.001$) with a sensitivity of 86.67 % and specificity of 83.33 % at a cutoff value of >1.7 . In conclusion, survivin mRNA expression and its serum level are elevated in patients with DR than those without DR. They showed strong positive correlation with HbA1c level. Both survivin mRNA expression and its serum level might have a marked role in the diagnosis of DR.

Keywords: Survivin expression, Serum survivin, Diabetic retinopathy.

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Introduction

Diabetes mellitus (DM) is a chronic disorder complicated by macrovascular and microvascular changes.¹ The International Diabetes Federation indicated that DM affected 537 million adults between 20 to 79 years worldwide increasing to 643 million in 2030. DM affects 73 million in Middle East and North Africa.² In Egypt, it was expected to increase from 5–10 % in the 1990s to > 13 % by 2025.³

The commonest microvascular complication is DR which may result in blindness. Many mechanisms can lead to vascular changes.⁴ Retinal neovascularization diagnose DR. It is either non-proliferative or proliferative.⁵ DR prevalence will rise due to the expected increased diabetic patient's life span.⁶ It varies greatly (7.6–60%) in Middle Eastern region, including Egypt.³

Ischemic process results from interacting complement factors, cytokines and mediators before the anatomical changes. Survivin is an anti-apoptotic protein controlling cellular proliferation.⁷ It is produced in fetal and malignant tissues but is seldomly expressed in normal tissues.⁸ Survivin inhibits endothelial cell apoptosis and improves angiogenesis.⁹ Diabetic vasculopathy increases survivin expression.¹⁰ Measuring blood or body fluids biomarkers help in understanding the pathological disorders.¹¹ In diabetics, several biomarkers level change in serum, tears, vitreous and aqueous humor.¹²⁻¹⁴

Survivin reflects DR severity. Serum survivin level is increased in non-proliferative DR than cases without DR.¹⁵ Survivin activates HIF-1 α pathway contributing to DR development and progression.¹⁶

We measured survivin expression by real time PCR in diabetic patients and its serum level by ELISA method as potential biomarkers of retinopathy in Egyptian diabetic patients.

Subjects and Methods

A case control study was carried out in ophthalmology, diabetic clinics and clinical pathology department.

Target population

Type 2 diabetic patients who visited the ophthalmology outpatient and diabetic clinics between Feb 2025 and July 2025 were recruited in the study using convenience sampling according to history taking, clinical examination and strict inclusion and exclusion criteria. We included 90 subjects in the study and classified them into 3 groups:

Group I: Thirty (30) patients with DR; group II: Thirty (30) patients without DR and group III: Thirty (30) healthy individuals serving as normal control group which was composed of employees and attendants for routine checkup with matched age and gender. Groups I and II were included according to the following criteria.

Inclusion criteria

Type 2 DM patients according to American Diabetes Association (ADA) criteria.¹⁷ Fasting blood glucose (FBG) ≥ 126 mg/dL or Random blood glucose (RBG) ≥ 200 mg/dL with hyperglycemic symptoms or crisis or 2-hr postprandial glucose (PPG) level ≥ 200 mg/dL or during a 75-g oral glucose tolerance test or Hemoglobin A 1c (HbA1c) level of $\geq 6.5\%$.

DR was diagnosed by the biomicroscopic fundus examination using the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.¹⁸ Accordingly, group I was classified into two subgroups:

Group Ia: DR cases with non-proliferative diabetic retinopathy (NPDR); n=17

Group Ib: DR cases with proliferative diabetic retinopathy (PDR); n=13

Control Group (Group III): Age- and sex-matched healthy attendants and employees with normal glucose tolerance (HbA1c <5.7% and FBG <100 mg/dL).

Exclusion criteria

Patients with any of the following conditions were strictly excluded:

-Any history or current presence of solid tumors or hematological malignancies

-Active systemic inflammatory conditions, rheumatologic diseases, inflammatory bowel disease, or type 1 DM.

-Ocular trauma, active ocular inflammation/uveitis, glaucoma, age-related macular degeneration, retinal vein/artery occlusion, or prior panretinal photocoagulation (PRP) / intravitreal anti-VEGF injections within the preceding 6 months.

-Uncontrolled hypertension, acute coronary syndrome, history of stroke, or advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m²).

-Active systemic infections, severe hepatic impairment, pregnancy or lactation, and current use of systemic immunosuppressive or cytotoxic therapy.

Data collection tools

Each participant filled a questionnaire including detailed medical history, the awareness of DR and its source, any preceding fundus examination and taken drugs. General examination including height, weight, body mass index (BMI), Ophthalmic examination, DR evaluation using Ophthalmoscope, BCVA, slit-lamp biomicroscopy and fundoscopy were performed by two experienced ophthalmologists who were fully blinded to the subjects' laboratory results to avoid diagnostic bias. DR grading strictly followed the International Clinical Diabetic Retinopathy Disease Severity Scale.¹⁸

A total of 10 mL of venous blood was withdrawn from each subject on two different occasions on the same day. After a 10-hour overnight fast, 5 mL of blood were drawn into a sterile plain tube, left to clot then centrifuged at 2,000–3,000 rpm for 10 minutes. The resulting serum was divided into two Eppendorf tubes: one was used for the measurement of FPG, and serum creatinine, while the other was kept at –20°C for later analysis of serum survivin using human survivin ELISA kit. Two hours after food intake (postprandial), another 5 mL blood was collected and distributed as: 2 mL in a sterile EDTA vacutainer for HbA1c measurement, 2 mL in a plain tube for 2-hour PPG and 1 mL in an EDTA tube for RNA extraction and PCR analysis.

A single voided spot urine sample was collected in a clean container for urinary albumin/creatinine ratio (UACR).

The chemical tests were done on Cobas 6000 automated analyzer, Roche Diagnostics, Mannheim, Germany). Estimated GFR (eGFR) was calculated by the following equation:

MDRD Calculation: $GFR = 175 \times ([\text{serum creatinine}]^{-1.154}) \times ([\text{age}]^{-0.203}) \times (0.742 \text{ for females})$.¹⁹ Urinary albumin/creatinine ratio (UACR) was classified as (in mg Albumin/g Creatinine): Normal: < 30; Microalbuminuria: 30–300; Macroalbuminuria: ACR > 300.²⁰

Survivin was measured by human Survivin ELISA Kits from (Bioassay technology laboratory 1008 Junjiang Inter. Bldg. 228 Ningguo Rd. Yangpu Dist. Shanghai. Cat.NoE3904Hu. China). Absorbance measurements were performed at 450 nm using a Microplate Reader (Statfax Technology, USA). The minimum detection limit for survivin was 2.490 pg/mL, with intra-assay and inter-assay coefficients of variation of <10 %. A standard curve was drawn and the sample concentration was calculated by plotting the samples OD on the standard curve.

Survivin mRNA from peripheral blood was done by using total RNA extraction kit (Quiagen Kit Rneasy, Germany). Nano-Drop ND-1000 spectrophotometer (Tech., Wilmington, DE, USA) was used to examine RNA purity. RNA was kept at –80°C for subsequent testing. Reverse transcription and amplification of survivin gene were done by real time PCR SuperScript III Reverse Transcriptase Kit (Invitrogen, Carlsbad, CA, USA) for cDNA. Our internal control was β -actin. We used SYBR Green Kit for Real-time PCR using a thermal cycler (Applied Biosystems Step One, USA). The primers sequences were: Survivin (forward: 5'-AGGACCACCGGATCTACACCTTCA-3, reverse: 5'-CTCGGTAGGGCAGTGGATGAAGC-3') and β -actin (forward: 5'-CACCATTGGCAATGAGCGGTTC-3', reverse: 5'-AGGTCTTTGGGATGTCCACGT-3').

The conditions for PCR reactions were: 1 min at 95°C, 35 cycles at 95°C for 10 seconds, 60°C for 30 seconds, and 72°C for 20 seconds. The qRT-PCR data were analyzed by the comparative

delta cycle threshold ΔCt method.²¹ $\Delta Ct = 2^{-X}$; $X = \Delta \Delta Ct = \Delta Ct (\text{experimental sample}) - \Delta Ct (\text{control sample}) = Ct (\text{experimental sample_housekeeping sample}) - Ct (\text{control sample_housekeeping sample})$

Statistical Analysis

Data was analyzed by IBM Statistical Package for the Social Science (SPSS) software package version 20.0. Independent t-test analyzed normally distributed data as mean $\pm$ standard deviation (SD) and Mann–Whitney U test analyzed non-normally distributed data and represented as median and interquartile range (IQR). Categorical variables were reported as count (n) and percentage (%) and analyzed

using Pearson chi-square test or Fisher's exact as appropriate. Correlating variables were carried out by Spearman correlation analysis. Receiver operating characteristic (ROC) curve determined the diagnostic performance. $p < 0.05$ with 95% confidence intervals points to result significance.

Results

A total of 60 diabetic patients and 30 healthy controls were included in the study. They were age and sex matched with no significant difference (Table 1). DM duration varied significantly between DR group and DM group without retinopathy.

Table 1. Different characteristics of the three studied groups.

	Group I (DR) n = 30	Group II (without DR) n = 30	Group III (Control) n = 30	p
Age				
Min. – Max.	42.0 – 60.0	42.0 – 62.0	42.0 – 60.0	^F NS
Mean $\pm$ SD.	50.0 $\pm$ 7.02	55.63 $\pm$ 7.09	50.63 $\pm$ 7.60	
Sig. bet. grps.	$p_1=0.09(\text{NS})$, $p_2=0.939(\text{NS})$, $p_3=0.064(\text{NS})$			
Gender				
Male	16 (53.3%)	17 (56.7%)	19 (63.3%)	^{x2} NS
Female	14 (46.7%)	13 (43.3%)	11 (36.7%)	
Duration of DM				
Min. – Max.	4.0 – 12.0	2.0 – 10.0	–	^U <0.001*
Mean $\pm$ SD.	9.23 $\pm$ 2.60	5.47 $\pm$ 1.59	–	

SD: Standard deviation

U: Mann Whitney test χ^2 : Chi square test

MC: Monte Carlo test

F: One way ANOVA test, Post Hoc Test (Tukey) was used for Pairwise comparison between each 2 groups.

H: Kruskal Wallis test, Post Hoc Test (Dunn's for multiple comparisons test)

p : p value between the three studied groups. p_1 : between diabetic retinopathy and without diabetic retinopathy

p_2 : between diabetic retinopathy and control. p_3 : between without Diabetic retinopathy and control.

* $p > 0.05$ is not significant (NS).

In Table (2), FBG, PPG, HbA1c, serum creatinine (mg/dl), UACR and eGFR were higher in DR

patients with a significant variation between the studied groups ($p < 0.001$).

Table 2. Comparison of biochemical parameters among the study groups.

	Group I (DR) n = 30	Group II (without DR) n = 30	Group III (Control) n = 30	<i>p</i>
FBG mg/dl				
Min. – Max.	110.0 – 340.0	110.0 – 280.0	90.0 – 119.0	^H <0.001*
Mean ± SD.	196.4 ± 56.29	147.2 ± 32.54	95.97 ± 6.26	
Sig. bet. grps.	$p_1=0.009^*$, $p_2<0.001^*$, $p_3<0.001^*$			
PPG mg/dl				
Min. – Max.	105.0 – 362.0	125.0 – 300.0	95.0 – 120.0	^F <0.001*
Mean ± SD.	243.9 ± 61.59	193.1 ± 41.30	106.1 ± 5.76	
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
Min. – Max.	7.80 – 14.50	5.80 – 8.0	4.0 – 5.50	^H <0.001*
Mean ± SD.	10.25 ± 1.17	7.25 ± 0.60	4.80 ± 0.43	
Sig. bet. grps.	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
S.Creatinine (mg/dl)				
Min. – Max.	0.60 – 1.10	0.60 – 0.90	0.40 – 1.0	^F <0.001*
Mean ± SD.	0.87 ± 0.13	0.75 ± 0.11	0.70 ± 0.17	
Sig. bet. grps.	$p_1=0.002^*$, $p_2<0.001^*$, $p_3=0.445(NS)$			
UACR (mg/g)				
Min. – Max.	14.0 – 360.0	13.0 – 250.0	16.0 – 34.0	^H <0.001*
Mean ± SD.	143.5 ± 123.1	48.80 ± 43.79	24.87 ± 4.10	
Sig. bet. grps.	$p_1=$, $p_2<0.001^*$, $p_3=0.012^*$			
eGFR				
Min. – Max.	70.0 – 146.0	79.0 – 130.0	91.0 – 141.0	^F <0.001*
Mean ± SD.	114.2 ± 19.35	103.6 ± 15.98	122.2 ± 12.0	
Sig. bet. grps.	$p_1=0.032^*$, $p_2=0.134(NS)$, $p_3<0.001^*$			

Fasting blood glucose (FBG), 2-hr postprandial glucose (PPG), Urinary albumin/creatinine ratio (UACR), Estimated GFR (eGFR), Hemoglobin A 1c (HbA1c). SD: Standard deviation

F: One way ANOVA test, Post Hoc Test (Tukey) was used for pairwise comparison between each 2 groups

H: Kruskal Wallis test, Post Hoc Test (Dunn's for multiple comparisons test)

p: *p* value between the three studied groups

p_1 : between diabetic retinopathy and without diabetic retinopathy. p_2 : between diabetic retinopathy and control

p_3 : between without diabetic retinopathy and control. **p* > 0.05 is not significant (NS).

The mean serum survivin level was 515.0 ng/l ± 76.77, 309.4 pg/mL ± 34.66 and 81.97 pg/mL ± 13.42 among DR patients, patients without DR and normal controls respectively. This variation was significant ($p<0.001$). The mean survivin

mRNA fold change in DR patients was 2.80 ± 0.46 compared to 1.42 ± 0.20 and 1.0 ± 0.0 in patients without DR and healthy controls respectively as shown in table 3.

Table 3. Serum survivin level and Survivin mRNA expression among the three studied groups.

	With Diabetic retinopathy	Without Diabetic retinopathy	Control	^F <i>p</i>
Survivin pg/mL				
Min. – Max.	310.0– 632.0	250.0 – 370.0	58.0 – 105.0	<0.001*
Mean ± SD.	515.0 ± 76.77	309.4 ± 34.66	81.97 ± 13.42	
Sig. bet. grps.	$p_1 < 0.001^*$, $p_2 < 0.001^*$, $p_3 < 0.001^*$			
Survivin mRNA				
Min. – Max.	1.90 – 3.60	1.10 – 1.80	1.0 – 1.0	<0.001*
Mean ± SD.	2.80 ± 0.46	1.42 ± 0.20	1.0 ± 0.0	
Sig. bet. grps.	$p_1 < 0.001^*$, $p_2 < 0.001^*$, $p_3 < 0.001^*$			

SD: Standard deviation. F: One way ANOVA test, Post Hoc Test (Tukey)

p: *p* value between the three studied groups. *p*₁: between diabetic retinopathy and without diabetic retinopathy*p*₂: between diabetic retinopathy and control. *p*₃: between without diabetic retinopathy and control*: Statistically significant at *p* ≤ 0.05.

Table 4 shows serum survivin was significantly higher in PDR than NPDR (516.8±72.78 pg/mL vs 313.6±81.89, *p*=0.002). However, there was no

difference in survivin mRNA levels between the two DR subtypes (2.62±0.70 vs 2.57±0.72, *p*=0.055).

Table 4. Serum survivin and its mRNA levels in diabetic retinopathy subtypes.

	DR group (n = 30)		<i>p</i>
	NPDR (n= 17)	PDR (n= 13)	
Survivin			
Min. – Max.	310.0 – 411.0	390.0 – 632.0	0.002
Mean ± SD.	313.6 ± 81.89	516.8 ± 72.78	
Survivin mRNA			
Min. – Max.	1.10 – 3.60	1.70 – 3.60	NS
Mean ± SD.	2.57 ± 0.72	2.62 ± 0.70	

SD: Standard deviation t: Student t-test. *p* > 0.05 is not significant (NS).

Table 5 showed a strong positive correlation between HbA1c level with serum survivin and its mRNA levels in overall DM patients (*p*<0.001)

while there is a lack of significance in diabetic subgroups: with and without DR (*p*=0.262, *p*=0.116 respectively).

Table 5. Correlation between HbA1c Level with serum survivin and Its mRNA levels between DM patients with and without DR.

	HbA1c %					
	DM		DR		Without DR	
	(Group I & Group II, n= 60)		(Group I, n = 30)		(Group II, n = 30)	
	<i>r</i> _s	<i>p</i>	<i>r</i> _s	<i>p</i>	<i>r</i> _s	<i>p</i>
Survivin	0.808	<0.001*	0.211	NS	0.293	NS
Survivin mRNA	0.618	<0.001*	0.020	NS	0.013	NS

*r*_s: Spearman coefficient. **p* > 0.05 is not significant (NS).

ROC analysis evaluated the effectiveness of survivin mRNA and serum survivin levels in distinguishing diabetic retinopathy in DM patients. The AUC for serum survivin was 0.985 (95 % CI 0. 955 – 1.0, both $p < 0.01$) with 96.67 % sensitivity and 93.33% specificity at a

cutoff value of >360 pg/mL. For survivin mRNA was 0.907 (95% CI 0.820 – 0.995, both $p < 0.01$) with a sensitivity of 86.67 % and a specificity of 83.33% at a cutoff value of >1.7, indicating good discriminative ability (Figure 1 and Table 6).

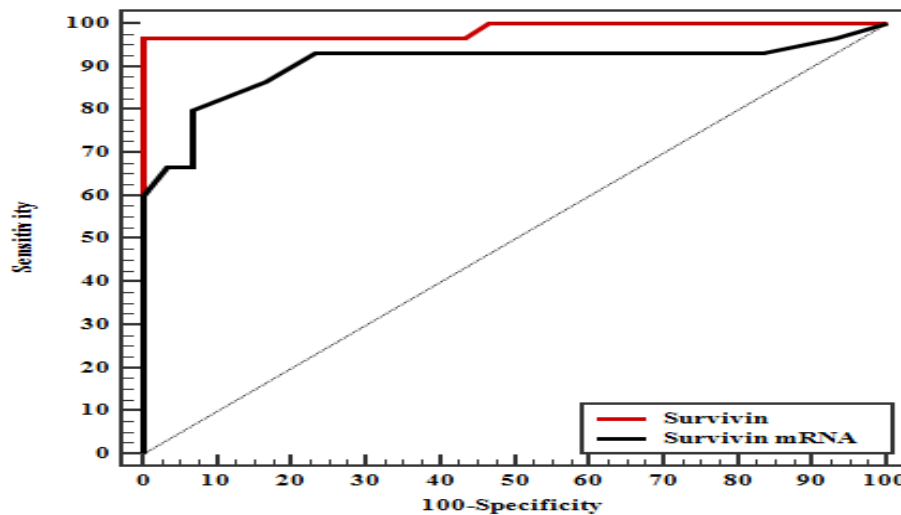


Figure 1. ROC curve for serum survivin and Survivin mRNA expression to differentiate DR cases (n = 30) from those without DR (n = 30)

Table 6. Diagnostic performance for Survivin mRNA and its serum levels to discriminate cases with DR (n = 30) from without DR (n = 30).

	AUC	P value	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Survivin	0.985	<0.001*	0.955 – 1.0	>360	96.67	93.33	93.5	96.6
Survivin mRNA	0.907	<0.001*	0.820 – 0.995	>1.7	86.67	83.33	83.9	86.2

AUC: Area Under a Curve. CI: Confidence Intervals. NPV: Negative predictive value. PPV: Positive predictive value.

*: Statistically significant at $p \leq 0.05$. #Cut off was chosen according to Youden index.

To determine whether serum survivin levels and survivin mRNA expression were independently associated with diabetic retinopathy after controlling the potential clinical and metabolic confounders, two multivariate binary logistic regression models were constructed (Table 7). Serum survivin remained a significant independent predictor of DR (aOR=1.042, 95%

CI: 1.012-1.073, $p=0.006$) alongside diabetes duration (aOR=1.669, $p=0.027$) and HbA1c (aOR=2.321, $p=0.044$). Survivin mRNA expression was independently associated with an increased risk of DR (aOR=4.210, 95% CI: 1.480-11.960, $p=0.007$). Confounders such as FBG, PPG, UACR, and eGFR did not reach statistical significance in the adjusted models.

Table 7. Multivariate binary logistic regression analysis for independent predictors of Diabetic Retinopathy (Group I vs. Group II).

Variable	β	Standard Error (SE)	p-value	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)
Serum Survivin					
Serum Survivin (pg/mL)	0.041	0.015	0.006*	1.042	1.012 – 1.073
DM Duration (years)	0.512	0.231	0.027*	1.669	1.061 – 2.625
HbA1c (%)	0.842	0.418	0.044*	2.321	1.022 – 5.268
FBG (mg/dL)	0.012	0.009	NS	1.012	0.994 – 1.030
PPG (mg/dL)	0.008	0.007	NS	1.008	0.994 – 1.022
UACR (mg/g)	0.006	0.004	NS	1.006	0.998 – 1.014
eGFR (mL/min/1.73)	-0.018	0.016	NS	0.982	0.952 – 1.013
Survivin Expression					
Survivin mRNA Expression	1.437	0.533	0.007*	4.210	1.480 – 11.960
DM Duration (years)	0.584	0.245	0.017*	1.793	1.109 – 2.900
HbA1c (%)	0.915	0.432	0.034*	2.497	1.071 – 5.821
FBG (mg/dL)	0.011	0.009	NS	1.011	0.993 – 1.029
PPG (mg/dL)	0.009	0.007	NS	1.009	0.995 – 1.023
UACR (mg/g)	0.005	0.004	NS	1.005	0.997 – 1.013
eGFR (mL/min/1.73)	-0.015	0.015	NS	0.985	0.956 – 1.015

Dependent Variable: Presence of Diabetic Retinopathy (0="Without DR", 1="With DR").

β : Unstandardized regression coefficient. SE: Standard Error. aOR: Adjusted Odds Ratio. CI: Confidence Interval

* $p > 0.05$ is not significant (NS).

Discussion

Type 2 DM is an endocrine disorder of chronic hyperglycemia, insulin resistance and over time reduced insulin production. It is a spreading worldwide health problem.^{22, 23} DR is a serious microvascular consequence which may lead to blindness.²⁴ Complex genetic and environmental factors affect T2DM susceptibility.²²

Survivin gene is located at chromosome 17q25.²⁴ Survivin is the smallest anti-apoptotic protein that mediates vascular remodeling and enhances cell survival.²⁵ Vascular damage and diabetic vasculopathy increase survivin expression.¹⁵

The detection of survivin and its mRNA expression in blood samples is preferable to other markers due to their widespread use and minimally invasive sampling technique.

Our results revealed that serum survivin level was more elevated in DR patients (515.0 ± 76.77 pg/ml) than patients without DR (309.4 ± 34.66 pg/mL). Its level was lowest in controls (81.97 ± 13.42 pg/mL) with a significant variation ($p < 0.001$).

Correspondingly, survivin mRNA expression was significantly variable between the studied groups ($p < 0.001$). Survivin mRNA normalized ratio was higher in DR cases followed by cases without DR then the control group (2.80 ± 0.46 , 1.42 ± 0.20 and 1.0 ± 0.0 respectively). Despite that, no difference in survivin mRNA levels between non-proliferative and proliferative subtypes. Serum survivin has higher sensitivity and specificity than survivin mRNA in discriminating patients with DR from those without DR (96.67, 93.33 and 86.67, 83.33, respectively).

Similar results were shown by Bilgin et al., 2024, suggesting that survivin level increases correspondingly with DR development. They found that the serum survivin were greater in non-proliferative retinopathy patients 54.92 ± 5.55 pg/mL than patients without DR 42.65 ± 5.37 pg/mL. Patients with proliferative DR had the lowest levels 37.46 ± 8.09 pg/mL, pointing to the most severe diabetic affection. They explained their findings as proliferative DR patients underwent panretinal photocoagulation for neovascularization. Survivin protein was lowest in proliferative DR patients as a result of retinal tissues ablation.¹⁵

Liu et al. confirmed that increased survivin expression stimulates retinal neovascularization and DR progression. They showed that the mRNA and survivin expression was normal in Wistar rats having DM for 3 months. Contrary, high survivin was found in the Wistar rats group with DM for 6 months suggesting that retinal ischemia and hypoxia results in increased survivin expression that subsequently increases cell proliferation, retinal angiogenesis, formation of a cellular vasculature and DR progression.¹⁶ Also, Cai et al. demonstrated that there was no survivin expression in normal retinal layers. Survivin protein was highly expressed in proliferative retinopathy retinas (2.56 ± 0.46 vs 3.34 ± 0.40 , $p < 0.01$).²⁷

Our results revealed that HbA1c level in diabetics was significantly correlated with serum survivin and its mRNA levels ($p < 0.001$). Similarly, a previous study revealed that hyperglycemia could lead to survivin overexpression. Survivin aggravates vascular endothelial cell dysfunction provoked by hyperglycemia.²⁸ High survivin mediates endothelial cell proliferation and angiogenesis.²⁹

This study had some limitations. Although strict exclusion criteria were implemented to eliminate major conditions influencing survivin levels (such as malignancies, systemic autoimmune diseases, active infections, and recent intravitreal therapies), subtle systemic subclinical inflammation or unmeasured metabolic factors could still act as minor confounders. The cross-sectional case-control design prevents establishing a direct causal relationship between circulating survivin levels

and the long-term progression of retinal vascular damage.

In conclusion, Elevated serum survivin and mRNA expression are strongly associated with the presence and severity of diabetic retinopathy in type 2 diabetic patients. While these findings highlight survivin as a potential biomarker and therapeutic target in retinal vascular injury, larger prospective longitudinal studies are required to confirm its clinical diagnostic utility and predictive value for DR progression.

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Author Contributions

All authors have seen and approved the manuscript, contributed significantly to the work. MG and MMK: concept, design, definition of intellectual content, literature search and clinical studies. HMM: data acquisition, data analysis, statistical analysis and literature search. SAA, DAA and MS: laboratory studies, literature search, data analysis, manuscript preparation, manuscript editing and manuscript review.

Declaration of Conflicting Interests

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Ethical approval

This study was approved by the ethical committee of faculty of medicine, Suez Canal University (No.5897#). All the study procedures followed Helsinki Declaration guidelines.

Informed consent

A signed consent form was obtained from each study participant.

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