Investigating the relationship between D-dimer serum level and diabetic retinopathy in patients with type 2 diabetes

Abstract

Background: Diabetic retinopathy (DR) is a major complication of type 2 diabetes (T2D) associated with microvascular damage and potential vision loss. D-dimer, a fibrin degradation product, serves as a marker of coagulation and fibrinolysis and may play a role in the development of DR (1). This study investigates the relationship between plasma D-dimer levels and the presence of DR in patients with T2D.

Methods: This cross-sectional descriptive-analytical study included 60 patients with T2D, divided into two groups: the DR group (n=30) and the non-DR group (n=30). Clinical and demographic data, including age, gender, duration of diabetes, medication use, and D-dimer levels, were collected and analyzed. Independent t-tests, Mann-Whitney tests, and univariate linear regression were employed for statistical analysis.

Results: The mean age of patients with DR was significantly higher than that of those without DR (57.60 ± 8.97 years vs. 51.33 ± 11.01 years, P=0.019). Univariate linear regression indicated a direct and significant relationship between D-dimer levels and DR (odds ratio: 0.34; P=0.009).

Conclusion: This study demonstrated that higher D-dimer levels are significantly associated with DR in T2D patients, along with older age, longer duration of diabetes, and distinct patterns of medication use. These findings suggest that D-dimer may be a potential biomarker for identifying T2D patients at greater risk for DR.

Keywords: Type Diabetic, Retinopathy, D-dimer

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INTRODUCTION

Diabetes mellitus is one of the most significant global health issues and is among the most common endocrine disorders(1, 2). It occurs at all ages and progresses chronically**,** imposing a substantial economic and social burden on healthcare systems worldwide, particularly in low- and middle-income countries where the prevalence is rising most rapidly (3)**.** Diabetes is categorized into two main types: Type 1 diabetes, which is associated with insufficient insulin secretion, and Type 2 diabetes, characterized by insulin resistance and impaired insulin function(4). These changes lead to metabolic and morphological disturbances in organs such as the kidneys, retina, and blood vessels, affecting nearly all body systems(5, 6).The global burden of diabetes is escalating at an alarming rate; according to the International Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, and this number is projected to reach 783 million by 2045, with Type 2 diabetes accounting for over 90% of all cases(7) .

The complications of Type 2 diabetes are divided into two main categories: microvascular complications (caused by damage to small blood vessels) and macrovascular complications (resulting from damage to larger blood vessels)(8). Microvascular complications include diabetic retinopathy (DR), diabetic nephropathy, cardiomyopathy, and diabetic neuropathy(9). Diabetic retinopathy is one of the most common microvascular complications and a leading cause of blindness among middle-aged and elderly individuals with diabetes(8, 9). According to the International Diabetes Federation, approximately 9.3% of the global population (463 million people) had diabetes in 2019, and this figure is projected to rise to 10.9% (700 million people) by 2045(10). In Iran, estimates indicate that about 11.5% of the population (over 3 million people) are affected by this disease(11).Among these, DR is not only one of the most common microvascular complications but also a leading cause of preventable blindness among working-age adults, significantly reducing patients' quality of life and contributing to increased socioeconomic costs (12)**.** According to the International Diabetes Federation, approximately 9.3% of the global population (463 million people) had diabetes in 2019, and this figure is projected to rise to 10.9% (700 million people) by 2045 (11). In Iran, estimates indicate that about 11.5% of the population (over 3 million people) are affected by this disease, highlighting the urgent need for region-specific strategies to combat its complications. Moreover, the prevalence of DR among diabetic patients is estimated to be approximately 22-27% in the Middle East and North Africa region, emphasizing the critical importance of identifying modifiable risk factors in this population (13, 14). Vascular complications of diabetes account for nearly 50% of mortality among diabetic patients in developed countries(15).

The underlying pathophysiology of these complications is a complex interplay of metabolic and hemodynamic factors, with chronic hyperglycemia serving as the primary initiator of a cascade of damaging events (16)**.** Strict glycemic control has been shown in some prospective studies to reduce the incidence and progression of microvascular complications in diabetic patients(17). However, a significant number of patients continue to develop complications despite optimal glycemic control, suggesting the involvement of additional factors beyond hyperglycemia, including genetic predisposition, oxidative stress, and chronic low-grade inflammation(18). Chronic hyperglycemia and associated inflammation lead to endothelial damage and impairment of vascular function. Endothelial dysfunction and increased coagulability are among the earliest signs of this process often preceding clinical manifestations by several years and contributing to a prothrombotic state that exacerbates microvascular occlusion and tissue hypoxia(17, 19). Therefore, identifying high-risk patients and finding effective strategies for preventing microvascular complications in diabetic patients is of great importance. One of the biomarkers that may be useful in predicting the risk of vascular complications in diabetic patients is D-dimer. D-dimer is a small peptide formed from fibrin degradation in blood clots and serves as an indicator of fibrinolytic activity. Elevated levels of D-dimer signify increased fibrin formation and a tendency toward thrombosis. This marker is routinely used in the diagnosis of vascular thrombosis; however, its elevation can also be observed in other conditions such as inflammation, cancer, liver disease, pregnancy, and post-surgery(20-22). Notably, in the context of diabetes, elevated D-dimer levels reflect not only a hypercoagulable state but also an impaired fibrinolytic capacity, which collectively contribute to the pathogenesis of microvascular damage (23).

Several studies have shown that diabetic patients with microvascular complications have higher levels of D-dimer compared to those without such complications. Kiran Shetty et al stated in their study that D-dimer could play a complementary role in the early diagnosis of diabetes complications and the progression of diabetic retinopathy (22). Additionally, Zhuang L et al. demonstrated a close

correlation between elevated plasma D-dimer levels and peripheral nerve dysfunction in diabetic patients(21). Additionally, elevated plasma D-dimer levels were identified as having an independent relationship with inflammation (measured by IL-6) and abnormal lipid profiles in individuals with type 2 diabetes (T2D)(16). Despite these promising findings, the exact mechanistic role of D-dimer in the pathogenesis of DR remains incompletely understood, and studies specifically investigating its association with different stages of DR (non-proliferative vs. proliferative) are limited and occasionally conflicting(24) . Furthermore, most existing studies have been conducted in Western or Asian populations, with a paucity of data from the Middle Eastern context, where genetic, dietary, and lifestyle factors may influence these associations (۲۵).Considering the importance of predicting and preventing microvascular complications in diabetic patients and the potential role of D-dimer as a biomarker, this study aims to investigate the relationship between plasma D-dimer levels and diabetic retinopathy in patients with Type 2 diabetes.

Materials & Methods

This cross-sectional study was conducted in 2024 at the Yasuj Diabetes Clinic, focusing on patients suffering from diabetic retinopathy among those with Type 2 diabetes who visited the clinic. The sampling method used in this research was simple random sampling or systematic sampling. The sample size was determined based on the study by Heng Zhao et al. (18) with an α of 0.05, 80% power, the mean and standard deviation of D-dimer in the retinopathy group (1.06 ± 0.54) and the non-retinopathy group (0.39 ± 0.21). An initial sample size of 6 was calculated for each group, and considering a 15% dropout rate, this was increased to 7 per group. To approximate a normal distribution of the variable, the sample size in each group was set at 30 patients.

Inclusion criteria for the study were complete consent to participate, age between 30 and 80 years, a diagnosis of diabetic retinopathy by an ophthalmologist, no use of medications with neurotoxic side effects, no history of venous thromboembolism or pulmonary embolism, and no use of anticoagulant or antiplatelet drugs in the past three months. Exclusion criteria included unwillingness to continue participation and failure to meet any of the inclusion criteria.

Data were collected through a demographic questionnaire, which included information on age, gender, education, living location, microvascular complications, and the duration of diabetes diagnosis. Measurements of D-dimer levels were obtained through venous sampling conducted by the researcher, using a 5 mL disposable syringe and collected in disposable tubes containing sodium citrate. Plasma was separated after centrifugation, and D-dimer levels were measured using the ELISA method.

Data analysis was performed using descriptive statistics, including means and standard deviations, as well as inferential statistics (independent t-tests for normally distributed continuous variables according to the Shapiro-Wilk test, or Mann-Whitney tests for non-normally distributed variables; Spearman correlation coefficient, and logistic regression to assess the predictive factors for retinopathy) utilizing SPSS software version 25. All statistical operations were considered significant at a p-value of < 0.05.

RESULTS

In this study, 60 patients with Type 2 diabetes were evaluated in two groups: those with retinopathy and those without retinopathy. The mean ± standard deviation of age for the control group and the retinopathy group was 51.33 ± 11.01 years and 57.60 ± 8.97 years, respectively. The results indicated a statistically significant difference in age between the two groups (P=0.019), with patients in the retinopathy group being significantly older. Our findings revealed that the control group had a higher percentage of metformin use compared to the retinopathy group (53.3% vs. 26.7%, P=0.035), while insulin use was lower in the control group (13.3% vs. 40.0%, P=0.020)(Table1).

Table1: Comparison of gender distribution, diabetes medication use, and underlying diseases between the two groups

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To compare the duration of diabetes between the two groups, the Mann-Whitney test was utilized, and the results showed a statistically significant difference in the average duration of diabetes between the two groups (P=0.001), with the duration of diabetes being significantly longer in patients with retinopathy.

Given the non-normal distribution of D-dimer levels (Kolmogorov-Smirnov test: P=0.001), the Mann-Whitney test was employed to compare D-dimer levels between the two groups. The results indicated a statistically significant difference in average D-dimer levels between the groups (P=0.001), with

Variable	Control Group			Retinopathy Group		Test Statistic	P-value
	Number		%	Number	%		
Gender	Female	٢٣	٧.٧٦	١٧	٧.٥٦	٧٠.٢	١.٠
	male	٧	٣.٢٣	١٣	٣.٤٣		
zipmet	No	٢١	٧٠	١٩	٣.٦٣	٣٠.٠	٥٨٤.٠
	Yes	٩	٣٠	١١	٧.٣٦		
Insulin	No	٢٦	٧.٨٦	١٨	٠.٦٠	٤٦.٥	٠٢٠.٠
	Yes	٤	٣.١٣	١٢	٠.٤٠		
Metformin	No	١٤	٧.٤٦	٢٢	٣.٧٣	٤٤.٤	٠٣٥.٠
	Yes	١٦	٣.٥٣	٨	٧.٢٦		
Gliclazide	No	٢٦	٧.٨٦	٢٨	٣.٩٣	٧٤.٠	٣٨٩.٠
	Yes	٤	٣.١٣	٢	٧.٦		
Peglotica	No	٢٨	٣.٩٣	٣٠	١٠٠	٠٧.٢	١٥٠.٠
	Yes	٢	٧.٦	٠	٠		
Comorbidity	No	١٢	٤.٤١	١١	٧.٣٦	١٣٨.٠	٧١١.٠
	Yes	١٧	٦.٥٨	١٩	٣.٦٣		
Hypothyroidism	No	٢٩	٧.٩٦	٣٠	١٠٠	٠٢.١	٣١٣.٠
	Yes	١	٣.٣	٠	٠		
Thrombocytopenia	No	٢٩	٧.٩٦	٢٩	٧.٩٦	٠٠	٩٩٩.>٠
	Yes	١	٣.٣	١	٣.٣		
HLP	No	٢٥	٣.٨٣	٢٣	٧.٧٦	٤٢.٠	٥١٩.٠
	No	٥	٧.١٦	٧	٣.٢٣		
Seizure	Yes	٢٩	٧.٩٦	٣٠	١٠٠	٠٢.١	٣١٣.٠
	No	١	٣.٣	٠	٠		
Hypertension	Yes	١٧	٧.٥٦	١٧	٧.٥٦	٠٠.٠	٩٩٩.>٠
	No	١٣	٣.٤٣	١٣	٣.٤٣		
CABG	Yes	٢٨	٣.٩٣	٢٨	٣.٩٣	٠٠.٠	٩٩٩.>٠
	No	٢	٧.٦	٢	٧.٦		
IHD	Yes	٣٠	١٠٠	٢٨	٣.٩٣	٠٠.٢	١٥٧.٠
	No	٠	٠	٢	٧.٦		

patients with retinopathy exhibiting significantly higher D-dimer levels. To examine the relationship between D-dimer levels and retinopathy, Spearman's rho correlation coefficient was used. The results revealed a significant direct correlation between retinopathy and D-dimer levels (correlation coefficient: 0.41; P=0.001). There was a significant direct relationship between retinopathy and D-dimer (P<0.05) (Table2). In order to assess the predictive factors for retinopathy, variables including age, gender, duration of diabetes, insulin use status, and metformin use were entered into a logistic regression model.

Table 2: Determination of predictive factors for retinopathy based on logistic regression

Variable	B	**Standard Error**	**df**	P-value	Odds Ratio	Confidence %٩٥ Interval	
						Lower	upper
Age	٠.٠٥٥	٠.٠٤٠	١	٠.١٧١	١.٠٥٧	٠.٩٧٦	١.١٤٤
*(١) Gender	٢.١٩٥	٠.٩٢٤	١	٠.٠١٨	٨.٩٧٨	١.٤٦٨	٥٤.٨٩٢
D-Dimer	٥.٦٦٨	٢.٥٨٤	١	٠.٠٢٨	٢٨٩.٥٧٩	١.٨٢٨	٤٥٨٦٥.٢٣٧
Insulin Use							

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MetforminUse	١.١٦٩	٠.٩١٠	١	٠.١٩٩	٣.٢١٨	٠.٥٤١	١٩.١٤٧
Diabetes duration	-١.٣٤٧	٠.٩٠٣	١	٠.١٣٦	٠.٢٦٠	٠.٠٤٤	١.٥٢٨
Constant	٠.١٢٠	٠.٠٦٧	١	٠.٠٧٢	١.١٢٨	٠.٩٨٩	١.٢٨٥
	-٦.٤٢٤	٢.١٣١	١	٠.٠٠٣	٠.٠٠٢		

Coding for Gender: Female = 0, Male = 1

The results indicated that women had approximately nine times higher odds of developing retinopathy compared to men.

For each one-unit increase in D-dimer levels, the odds of developing retinopathy increased by about 290 times.

Figure 1: The ROC curve illustrates the predictive power of D-dimer levels regarding diabetic retinopathy complications. Based on the findings, the area under the curve (AUC) was 74%, indicating a 74% probability of accurately identifying samples. Furthermore, given that the p-value was less than 0.05, this finding is statistically significant, highlighting the effectiveness of D-dimer levels in predicting diabetic retinopathy complications at a meaningful level.

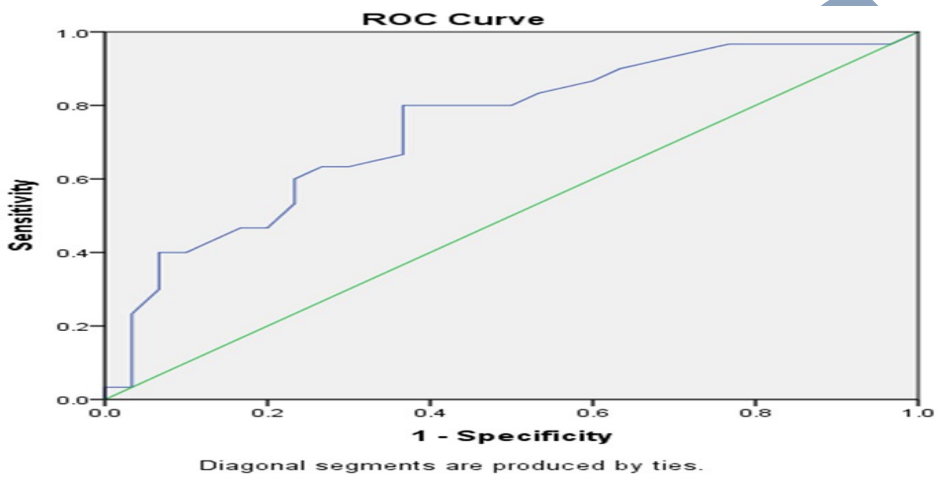

Figure 1: ROC Curve for the Predictive Power of D-dimer Levels in Diabetic Retinopathy Complications

Table 3: Results of the ROC Curve Analyzing the Predictive Power of D-dimer Levels in Diabetic Retinopathy Complications

AUC	Standard Error	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
٠/٧٤	٠/٠٦	٠/٠٠١	٠/٦١	٠/٨٧

The results related to sensitivity and specificity of D-dimer levels for predicting diabetic retinopathy are displayed in Table 3. At a cut-off value of 0.21, the test shows the highest sensitivity (80%) and the lowest false positive rate (36%). D-dimer levels equal to or greater than 0.21 indicate the presence of diabetic retinopathy (Table3).

DISCUSSION

Diabetic retinopathy stands as the most common microvascular complication of diabetes, though its underlying pathology remains incompletely elucidated. Both the duration and severity of hyperglycemia significantly influence the likelihood of developing diabetic retinopathy and other diabetes-related microvascular complications (26, 27). This condition is characterized by impaired retinal perfusion resulting from hyperglycemia-induced microvascular alterations in the retinal vasculature. In its proliferative form, abnormal neovascularization occurs on the optic disc or elsewhere in the retina(28).

This study compared clinical and biochemical parameters between two groups of patients with type 2 diabetes (T2D). The findings indicated that patients with diabetic retinopathy (DR) were older, had a longer duration of diabetes, and exhibited higher levels of D-dimer compared to those without DR.

Significant differences in medication usage were also observed; the DR group had lower metformin consumption and greater insulin use. Notably, the distribution of gender and the presence of comorbidities did not differ significantly between the two groups.

In the study by Zhuang et al.(21), which investigated the relationship between plasma D-dimer levels and diabetic peripheral neuropathy (DPN) in patients with type 2 diabetes, the findings demonstrated a strong association between elevated D-dimer levels and peripheral nerve dysfunction, thereby introducing D-dimer as a promising biomarker for DPN. The results of this study align with those of the current investigation. Both studies emphasize D-dimer as a marker of vascular diseases in diabetes. Their focus on DPN complements our emphasis on diabetic retinopathy (DR), as both conditions involve microvascular damage. This broader perspective strengthens the evidence for utilizing D-dimer as a general predictor of diabetic microangiopathies and further validates your findings.

Cheng et al.(20) conducted a retrospective cohort study to evaluate the role of D-dimer as a predictor of cardiovascular outcomes in patients with type 2 diabetes. This study revealed that elevated D-dimer levels were predictive of cardiovascular complications and highlighted its role as a risk stratification tool. The positive correlation with HbA1c in Cheng et al.'s findings provides additional support for the high D-dimer levels observed in DR, as chronic hyperglycemia is the underlying factor for both microvascular and macrovascular complications. However, Cheng et al. emphasized macrovascular disease, while the current study focused on microvascular pathology. This distinction illustrates the versatility of D-dimer as a biomarker across a spectrum of vascular complications in diabetes.

The study by Shetty et al. (31) demonstrated that elevated D-dimer levels were significantly associated with advanced stages of diabetic retinopathy (DR) and high HbA1c levels. The findings of Shati et al. are directly consistent with the present study, as both highlight the importance of D-dimer in the progression of DR and its potential as an early diagnostic marker. The observed association with HbA1c aligns with the pathophysiological link between hyperglycemia and microvascular damage.

In a study conducted by Heng Zhao et al(29) .Levels of HbA1c, D-dimer, and fibrinogen were analyzed in 61 diabetic patients at various stages of DR. Higher levels of these markers were observed in proliferative diabetic retinopathy (PDR) compared to non-proliferative diabetic retinopathy (NPDR) and no-DR groups. The combined measurement of these markers improved the early diagnosis of microvascular damage. The findings of Zhao et al. complement our study, further supporting D-dimer as a marker of DR severity. The results of the study by Olga et al.(30) showed that there is a positive association between D-Dimer levels and stages of diabetic retinopathy, which is consistent with the present study.

Collectively, these studies validate D-dimer as a key biomarker for vascular complications in diabetes. While each study focuses on different complications—neuropathy, nephropathy, cardiovascular disease, and retinopathy—they converge on a common theme: elevated D-dimer levels indicate hypercoagulability and endothelial dysfunction related to the pathophysiology of diabetes. The consistency of the findings across studies justifies the emphasis of the present study on D-dimer in DR and demonstrates its broader applicability as a risk stratification tool for diabetic complications. Overall, this study highlights a significant relationship between elevated D-dimer levels and the presence of DR in patients with T2D, suggesting that D-dimer could serve as a potential biomarker for identifying patients at higher risk of DR. The findings underscore the importance of early screening and monitoring of coagulopathy abnormalities in diabetes management.

Conclusion

The results indicate that higher D-dimer levels are significantly associated with the presence of DR. Patients with DR have, on average, a higher age and a longer duration of diabetes. Significant differences were also observed in medication usage patterns between the two groups, with a lower use of metformin and higher insulin use in the DR group. Univariate linear regression further confirmed that D-dimer levels are directly and significantly related to DR. These findings suggest that D-dimer could be utilized as a potential biomarker for identifying T2D patients who are at increased risk for developing DR. The results emphasize the importance of monitoring D-dimer levels in the management of diabetic patients and preventing microvascular complications such as retinopathy.

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