RESEARCH ARTICLE

Correlation between plasma fibrinogen levels and microvascular complications in type 2 diabetes

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Abstract

Objective: To determine how plasma fibrinogen levels impact the severity of microvascular complications in people with type 2 diabetes while focussing on the molecular mechanisms of fibrinogen's role in such complications.

Method: The analytical, cross-sectional study was conducted from September 2022 to March 2023 at the Department of Medicine, Mardan Medical Complex and Teaching Hospital, Khyber Pakhtunkhwa, Pakistan, and comprised adult patients of either gender who had been diagnosed with type 2 diabetes and microvascular complications. Each patient was subjected to an evaluation of microvascular complications, including diabetic retinopathy, nephropathy and neuropathy, using validated diagnostic criteria and clinical examinations. Data was analysed using SPSS 26.

Results: Of the 174 patients 97(%) were males and 77(%) were females. Retinopathy was found in 57(32.7) patients with median age 53 years (interquartile range: 46-63 years). Nephropathy was found in 55(31.6%) subjects with median age 54 years (interquartile range: 50-61 years). Neuropathy was found in 62(35.6%) patients with median age 53 years (interquartile range: 48-58 years). Diabetic neuropathy was significantly associated with elevated plasma fibrinogen levels and various biomarkers, such as creatinine, urea, fasting blood glucose, glycated haemoglobin and estimated average glucose ($p<0.05$). Diabetic retinopathy was significantly linked with higher levels of fibrinogen, which manifested through symptoms, like floaters or dark spots, impaired colour vision, difficulty seeing at night, blurred or fluctuating vision and vision loss ($p<0.05$). Diabetic nephropathy and the progression of its severity was significantly associated with increased fibrinogen levels, as well as markers, like albuminuria, creatinine, urea, fasting blood glucose, glycated haemoglobin and estimated average glucose ($p<0.05$).

Conclusion: Elevated plasma fibrinogen levels in patients with type 2 diabetes significantly correlated with increased microvascular complications, underscoring the importance of monitoring and managing fibrinogen levels to mitigate diabetes-associated vascular pathologies.

Keywords: Diabetes mellitus, Microvascular complications, Serum fibrinogen, Nephropathy, Retinopathy, Neuropathy.

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Introduction

About 90% of all adult diabetics worldwide have type 2 diabetes mellitus (T2DM), which affects 537 million people.[1] After China and India, Pakistan ranks third globally in terms of the prevalence of diabetes.[2] Due to its increasing prevalence worldwide, T2DM is a chronic condition characterised by persistent hyperglycaemia driven on by insulin resistance (IR).[3] Microvascular complications (MVCs), including diabetic retinopathy, nephropathy and neuropathy, are among the many complications the metabolic disease can cause. If left untreated, these issues can result in irreparable organ damage as well as disability.[4,5]

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Studies have shown that the beginning of these complications in T2DM and elevated plasma fibrinogen levels are related. Fibrinogen, a vital component of the coagulation cascade, has been related to endothelial dysfunction and hypercoagulability, which are factors crucial to the pathogenesis of diabetic MVCs. Plasma fibrinogen levels are frequently raised in diabetic individuals with MVCs and have been linked to poor glycaemic control.[6,7]

The most common cause of adult blindness is diabetic retinopathy, which is characterised by damage to the blood vessels in the retina.[8] The fragile microvasculature of the retina can be damaged by fibrinogen's involvement in encouraging the production of blood clots and thrombi, which can result in diabetic retinopathy. Similarly, nephropathy, a type of kidney disease triggered on by injury to the small blood vessels in the kidneys, is a significant contributor to kidney failure globally. Nephropathy is thought to be caused by a similar pathophysiological mechanism, in which fibrinogen-induced endothelial dysfunction and glomerular injury are key factors.[9]

Pain, numbness and even loss of sensation are common effects of neuropathy, often resulting from peripheral nerve injury. Recent studies suggest that factors, such as the permeability of the blood-brain barrier and the neuroinflammatory properties of fibrinogen, may contribute significantly to the development of neuropathic conditions in individuals with T2DM.[10]

The precise molecular mechanism through which plasma fibrinogen affects the beginning and development of different MVCs remain unclear. It is also not known whether changing plasma fibrinogen levels have an impact on the severity and prognosis of retinopathy, nephropathy and neuropathy in T2DM. The current study was planned to fill the gaps by examining the molecular mechanisms and the various effects of plasma fibrinogen levels on particular microvascular problems in people with T2DM.

Patients and Methods

The analytical, cross-sectional study was conducted from September 2022 to March 2023 at the Department of Medicine, Mardan Medical Complex and Teaching Hospital, Khyber Pakhtunkhwa, Pakistan. After approval from the ethics review board of Bacha Khan Medical College, Mardan, Pakistan, the sample size was calculated with 80% power and significance level 5%. The expected effect size and variability (standard deviation) of fibrinogen levels were estimated from preliminary data and relevant literature.[11]

The sample was raised using convenience sampling technique. Those included were adult T2DM patients diagnosed with a single MVC from among diabetic retinopathy, nephropathy and neuropathy. Patients age <18 years, those whose laboratory testing and assessment data was lacking, and those who had multiple MVCs were excluded.

After taking informed consent from the patients, data was collected about demographics, diabetes medication history, and other relevant clinical parameters, such as blood pressure, body mass index (BMI), while signs and symptoms were thoroughly examined. Patients had their MVCs evaluated through clinical tests and accepted diagnostic criteria. The severity and presence of the complications were assessed..

Diabetic retinopathy was diagnosed based on the presence and severity of retinal abnormalities, such as microaneurysms, haemorrhages, exudates, and new vessel formats. The American Academy of Ophthalmology (AAO) and National Eye Institute (NEI) guidelines were used to classify the stages of diabetic retinopathy into mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy.[12,13]

Based on albuminuria levels, diabetic nephropathy was diagnosed and staged in accordance with the recommendations of the American Diabetes Association (ADA) and the kidney disease: Improving Global Outcomes (KDIGO). The severity was divided into stages, such as normoalbuminuria, microalbuminuria and macroalbuminuria.[14-16]

Neurological examinations, such as nerve conduction investigations, monofilament testing and autonomic function tests, were used to assess diabetic neuropathy in the patients. Clinical signs of peripheral nerve injury, such as sensory loss, aberrant reflexes, muscle weakness and autonomic dysfunction, were used to assess the presence and severity of diabetic neuropathy. Based on the intensity and effect of neuropathic symptoms, severity was categorised as mild, moderate or severe.[17,18]

Blood samples were collected to measure plasma fibrinogen levels using a coagulometer (Helena Bioscience C-series) made in United Kingdom. Additional laboratory tests, including glycated haemoglobin (HbA1c), estimated average glucose (eAG), fasting blood glucose (FBG), creatinine, urea and urinary albumin levels, were performed (Roche Cobas e411 and c111) made in Switzerland to account for potential confounders.

Data was analysed using SPSS 26. Categorical variables were expressed as frequencies and percentages, and were assessed for differences using the chi-square test. Continuous variables, due to their non-normal distribution, were expressed as median and interquartile range (IQR), and compared across groups using the Kruskal-Wallis test. For analysing the association between plasma fibrinogen levels and the severity of MVCs, simple linear regression was used for outcomes that followed a normal distribution, with adjustments made for relevant covariates. $P<0.05$ was considered statistically significant.

Results

Of the 174 patients 97(%) were males and 77(%) were females. Retinopathy was found in 57(32.7) patients with median age 53 years (IQR: 46-63 years). Nephropathy was found in 55(31.6%) subjects with median age 54 years (IQR: 50-61 years). Neuropathy was found in 62(35.6%) patients with median age 53 years (IQR: 48-58 years).

Retinopathy severity was mild non-proliferative in 21(36.8%) patients, moderate non-proliferative in 26(45.6%), severe non-proliferative in 6(10.5%) and proliferative in 4(7%). Common symptoms included floaters

or dark patches, decreased colour vision, night vision difficulties and blurred vision, with 10(17.54%) patients experiencing severe vision loss or blindness (Table 1).

Increased retinopathy severity was linked with higher levels of fibrinogen, creatinine, FBG, HbA1c and eAG (Table 2).

Fibrinogen levels were positively correlated with retinopathy severity ($p<0.001$), and creatinine, FBG, HbA1c, eAG, blurred vision, floaters, night vision issues, colour vision impairment and vision loss were significant predictors of higher fibrinogen levels in diabetic retinopathy patients (Table 3).

Diabetic nephropathy severity was classified as normoalbuminuria 8(14.54%), microalbuminuria 32(58.18%) and macroalbuminuria 15(27.27%). Common symptoms included frequent urination and weakness, foamy urine, swelling in extremities, loss of appetite, nausea/vomiting and blood in urine (Table 4).

As the severity of diabetic nephropathy increased, so did the levels of fibrinogen, albuminuria, creatinine, urea, FBG, HbA1c and eAG (Table 5).

In patients with diabetic nephropathy, there was no significant link of plasma fibrinogen level with gender, diastolic blood pressure (DBP, systolic blood pressure (SBP), diabetes duration and medication used (Table 6).

Diabetic neuropathy severity was mild in 11(17.74%) patients, moderate in 31(50%) and severe in 20(32.25%). Common symptoms included numbness or tingling in extremities, digestive issues and sexual dysfunction (Table 7).

Plasma fibrinogen levels increased with increase in the levels of creatinine, blood urea, FBG, HbA1c and eAG (Table 8)

In patients with diabetic neuropathy, plasma fibrinogen levels significantly correlated with the degree of neuropathy severity, specific neuropathic symptoms, BMI, blood pressure levels, creatinine, blood urea, FBG, HbA1c and eAG (Table 9).

Molecular mechanisms by which fibrinogen influenced the development and progression of MVCs were also studied in detail (Figure).

Table-1: Demographics and clinical characteristics of patients with diabetic retinopathy (n=174).

Characteristics	n (%)
Retinopathy patients	57(32.75)
Age (years)	53(46-63)
Gender	
Male	27(47.36)
Female	30(52.64)
Body mass index (BMI)	
<18.5	4(7.01)
18.5-24.9	15(26.31)
25.0-29.9	14(24.56)
30.0-39.9	21(36.84)
>40.0	3(5.26)
Blood pressure	
Diastolic pressure	101(97-111)
Systolic pressure	139(131-158)
Diabetes duration	13(11-16)
Medication used	
Oral	38(66.66)
Insulin	19(33.33)
Patients severity	
Mild Non-proliferative	21(36.84)
Moderate Non-proliferative	26(45.61)
Severe Non-proliferative	6(10.52)
Proliferative	4(7.01)
Sign symptoms	
Blurred or fluctuating vision	45(78.94)
Floaters or dark spots in the field of vision	52(91.22)
Difficulty seeing at night	47(82.45)
Impaired colour vision	50(87.71)
Vision loss or blindness in severe cases	10(17.54)

Data is presented as frequency and percentage or as median and interquartile range.

Discussion

One of the primary findings of the current study was the significant association between elevated plasma fibrinogen levels and the severity of MVCs in T2DM patients.

Table-2: Comparison of plasma fibrinogen levels and biomarkers across different stages of diabetic retinopathy severity.

Severity	Mild Non-proliferative[1]	Moderate Non-proliferative[2]	Severe Non-proliferative[3]	Proliferative[4]	*p*-value
Total patients	21(36.84)	26(45.61)	6(10.52)	4(7.01)	
Fibrinogen	426(373-504)	534(463-615)	672(530-726)	699(678-719)	0.00
Creatinine	1.21(1.07-1.28)	1.22(1.13-1.31)	1.49(1.31-1.57)	1.50(1.48-1.52)	0.00
Urea	40.22(37.13-43.73)	41.67(37.11-44.63)	42.87(36.92-46.56)	44.31(41.11-45.91)	0.31
FBG	103(99-109)	118(111-122)	124(119-133)	129(125-131)	0.00
HbA1c	7.65(7.23-8.17)	10.28(9.78-10.71)	12.37(11.6-13.21)	12.89(12.77-12.95)	0.00
eAG	172(160-187)	248(233-260)	308(286-332)	323(319-324)	0.00

Data is presented as frequency and percentage or as median and interquartile range. FBG: Fasting blood glucose, HbA1c: Glycated haemoglobin, eAG: Estimated average glucose. $p<0.05$ was statically significant,

Table-3: Simple linear regression analysis of factors associated with plasma fibrinogen levels in patients with diabetic retinopathy.

Independent variables	Unstandardised Coefficients		Standardised Coefficients	*t*-value	*p*-value	95% CI for B	
	B	Std. Error	correlation			Lower	Upper
Age (1-year)	-2.15	2.08	-.138	-1.03	0.306	-6.33	2.02
Gender (Male)	-2.26	28.45	-.11	-.80	0.937	-59.28	54.78
Body mass index (BMI) kg/m^2	3.044	2.066	.415	0.97	0.044	1.09	5.14
Blood Pressure							
Diastolic pressure (1mmhg)	1.51	0.78	.312	1.93	0.031	0.89	4.31
Systolic pressure (1mmhg)	2.32	0.91	.499	2.54	0.024	1.63	3.01
Diabetes duration (1-year)	-2.837	7.34	-.052	-.386	0.701	-17.55	11.87
Medication used (Oral)	3.94	30.13	.018	.131	0.896	-56.44	64.33
Retinopathy severity (1 point)	100.15	14.69	.791	6.81	0.000	70.69	129.61
Sign symptoms							
Blurred or fluctuating vision (P)	129.65	60.14	.602	4.30	0.000	69.23	190.06
Floaters or dark spots in the field of vision (P)	79.25	49.07	.513	1.61	0.041	19.23	121.36
Difficulty seeing at night (P)	116.31	33.90	.523	3.43	0.001	48.36	184.25
Impaired colour vision (P)	95.39	41.33	.497	2.03	0.025	52.55	187.23
Vision loss or blindness in severe cases (P)	144.55	31.86	.622	4.53	0.000	80.69	208.45
Biomarkers							
Creatinine (1 mg/dl)	278.33	79.68	.521	3.48	0.001	177.99	438.54
Urea (1 mg/dl)	1.87	2.67	.094	0.68	0.481	-3.42	7.23
Fasting blood glucose (1 mg/dl)	5.38	1.08	.599	4.94	0.000	3.20	7.55
HbA1c (1 %)	30.65	6.72	.624	4.55	0.000	17.17	44.14
Estimated average glucose (1 mg/dl)	1.06	0.24	.626	4.55	0.000	0.58	1.53

Dependent Variable: fibrinogen; (P): symptoms present, HbA1c: Glycated haemoglobin, CI: Confidence interval. $p<0.05$ was statically significant.

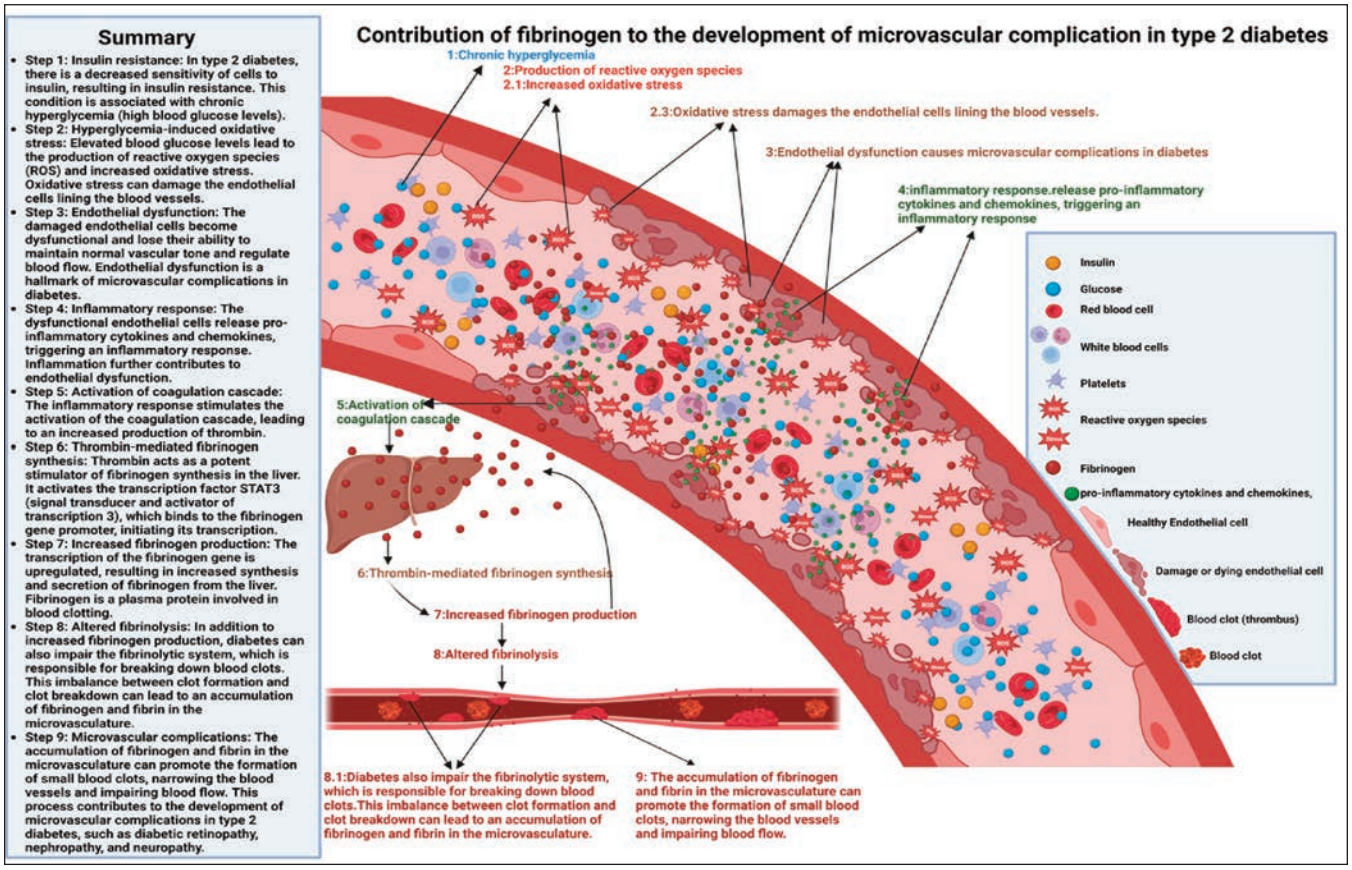

Figure: Molecular mechanisms of fibrinogen's role in microvascular complications (MVCs).

The results were consistent with earlier findings.[19-21]

In the current study, the age categories were specifically identified with respect to the MVC noted. The age distribution aligned with the age-related patterns of MVCs in T2DM patients.[22] underlining the positive correlation between age MVCs.

The current findings also suggested that an extended period of diabetes was associated with an increased likelihood of MVCs which was in line with literature.[23]

The current study found a notable association between MVCs and elevated median BMI among T2DM patients. The findings indicated a moderate connection between the levels of fibrinogen and BMI in individuals with retinopathy. A significant correlation was seen between the BMI of individuals with neuropathy and the severity of their ailment. An earlier study observed a connection between fibrinogen level and BMI in both overweight and normal healthy controls. The overweight individuals had fibrinogen levels of 564±129, whereas the healthy controls had fibrinogen levels of 433±139. However, the study did not specifically investigate the associations between different levels of fibrinogen, BMI and the severity of sub-types of MVCs.[24]

In the current study, a significant correlation was observed between fibrinogen levels and different biomarkers. However, a clear correlation between urea levels and the severity of retinopathy was not observed. The substantial concentrations of these indicators implied a potential correlation between fibrinogen and glycaemic control. The potential association between urine albumin, a biomarker for kidney impairment, and fibrinogen suggested the potential involvement of fibrinogen in the pathogenesis of diabetic nephropathy. Elevated levels of fibrinogen have the potential to contribute to the progression of nephropathy through the induction of glomerular damage and subsequent leaking of albumin into the urine. This finding was consistent with earlier studies.[24,25]

Limitations: The current study had several limitations. First, the study employed a cross-sectional design, which only provided a snapshot of the data at a specific point in time, and limited the ability to establish causal relationships or track changes over time. Longitudinal studies would be beneficial in understanding the dynamics of fibrinogen and their association with MVC in T2DM patients. Second, the limited sample size and the single-centre nature of the

Table-4: Demographics and clinical characteristics of study patients with diabetic nephropathy (n=174).

Characteristics	n (%)
Nephropathy patients	55(31.60)
Age (years)	54(50-61)
Gender	
Male	36(65.45)
Female	19(34.54)
Body mass index (BMI) kg/m^2	31(26-34)
<18.5	00(0.00)
18.5-24.9	10(18.18)
25.0-29.9	14(25.45)
30.0-39.9	28(50.90)
>40.0	03(5.45)
Blood pressure	
Diastolic pressure	105(97-121)
Systolic pressure	155(137-195)
Diabetes duration	17.0(13.0-19.0)
Medication used	
Oral	19(34.54)
Insulin	36(65.45)
Patients severity	
Normoalbumnuniria	08(14.54)
Microalbuminuria	32(58.18)
Macro albuminuria	15(27.27)
Sign symptoms	
Swelling (oedema) in the legs, ankles, feet, or hands	45(81.81)
Increased frequency of urination	51(92.72)
Foamy or bubbly urine	52(94.54)
Blood in urine	14(24.45)
Fatigue or weakness	51(92.72)
Loss of appetite	35(63.63)
Nausea or vomiting	30(54.54)

Data is presented as frequency and percentage or as median and interquartile range. *

Table-5: Comparison of plasma fibrinogen levels and biomarkers across different stages of diabetic nephropathy severity.

Severity	Normoalbumnuniria[1]	Microalbuminuria[2]	Macro albuminuria[3]	*p*-value
Total patients	08(14.54)	32(58.18)	15(27.27)	
Fibrinogen	433(388-492)	560(482-597)	677(591-723)	0.000
Albuminuria	14(11-20)	146(69-119)	422(369-484)	0.000
Creatinine	0.88(0.87-0.91)	1.14(1.04-1.36)	1.59(1.09-1.67)	0.000
Urea	31.95(31.47-32.75)	37.20(34.80-41.13)	48.60(41.57-50.37)	0.000
FBG	111(108-116)	119(112-129)	139(131-145)	0.000
Hba1c	9.16(9.0-9.20)	11.63(11.11-12.26)	12.76(11.34-13.10)	0.000
eAG	216(213-217)	287(272-305)	320(279-329)	0.000

Data is presented as frequency and percentage or as median and interquartile range. FBG: Fasting blood glucose, HbA1c: Glycated haemoglobin, eAG: Estimated average glucose. $p<0.05$ was statically significant.

Table-6: Simple linear regression analysis of factors associated with plasma fibrinogen levels in patients with diabetic nephropathy.

Model	Unstandardised Coefficients		Standardised Coefficients correlation	*t*-value	*p*-value	95% CI for B	
	B	Std. Error				Lower	Upper
Age (1-year)	3.99	1.77	.296	2.25	0.028	0.441	7.546
Gender (Male)	28.94	28.35	.139	1.02	0.312	-27.39	85.81
Body mass index (1 kg/m^2)	5.57	2.53	.398	2.27	0.027	0.67	10.83
Blood pressure							
Diastolic pressure (1 mmhg)	0.23	1.21	.026	0.19	0.849	-2.21	2.67
Systolic pressure (1 mmhg)	0.86	0.70	.166	1.22	0.226	-0.549	2.27
Diabetes duration (1-year)	0.37	4.95	.010	0.075	0.940	-9.55	10.30
Medication used (Oral)	45.04	29.10	.208	1.54	0.128	-13.33	103.42
Patients severity (1 point)	108.43	16.96	.760	6.39	0.000	74.46	142.50
Sign symptoms							
Swelling (oedema) in the legs, ankles, feet, or hands (P)	97.24	34.62	.462	2.80	0.007	27.79	166.96
Increased frequency of urination (P)	143.01	51.50	.451	2.77	0.008	39.71	246.31
Foamy or bubbly urine (P)	125.31	60.61	.374	2.07	0.023	4.31	247.47
Blood in urine (P)	138.51	28.93	.661	4.80	0.000	80.92	196.97
Fatigue or weakness (P)	143.65	51.50	.494	2.77	0.008	39.71	246.31
Loss of appetite (P)	74.92	27.60	.351	2.71	0.009	19.54	130.29
Nausea or vomiting (P)	79.13	26.61	.379	2.97	0.004	25.75	132.51
Biomarkers							
Creatinine (1 mg/dl)	176.73	47.20	.612	3.74	0.000	81.98	271.48
Urea (1 mg/dl)	9.15	1.85	.592	4.92	0.000	5.43	12.86
Fasting blood glucose (1 mg/dl)	3.35	1.02	.512	3.26	0.002	1.29	5.54
HbA1c (1 %)	41.82	9.13	.632	4.58	0.000	23.15	60.14
Estimated average glucose (1 mg/dl)	1.45	0.13	.611	4.58	0.000	0.819	2.09

Dependent Variable: fibrinogen; P: Symptoms present, HbA1c: Glycated haemoglobin, CI: Confidence interval. P<0.05 was statically significant.

Table-7: Demographics and clinical characteristics of study patients with diabetic neuropathy (n=174).

Characteristics	n (%)
Neuropathy patients	62(35.63)
Age (years)	53(48-58)
Gender	
Male	34(54.83)
Female	28(45.17)
Body mass index (BMI) kg/m^2	32(28-38)
<18.5	00(0.00)
18.5-24.9	00(0.00)
25.0-29.9	24(38.70)
30.0-39.9	27(43.54)
>40.0	11(17.74
Blood pressure	
Diastolic pressure	132(120-137)
Systolic pressure	89(84-93)
Diabetes duration	16(14-20)
Medication used	
Oral	32(51.61)
Insulin	30(48.38)
Patients severity	
Mild	11(17.74)
Moderate	31(50.00)
Severe	20(32.25)

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Table-7: *Continued from previous column.....*

Characteristics	n (%)
Sign symptoms	
Numbness, tingling, or burning sensation in the hands, feet, or legs	50(80.64)
Sharp or shooting pains	20(32.25)
Loss of sensation	40(64.51)
Muscle weakness or loss of coordination	24(38.70)
Digestive issues like bloating, constipation, or diarrhoea	46(72.19)
Sexual dysfunction or decreased sexual response	45(72.58)

Data is presented as frequency and percentage or as median and interquartile range.

Table-8: Comparison of plasma fibrinogen levels and biomarkers across different stages of diabetic neuropathy severity.

Severity	Mild[1]	Moderate[2]	Severe[3]	*p*-value
Total patients	11(17.74)	31(50.00)	20(32.25)	
Fibrinogen	380(372-401)	453(424-490)	549(509-578)	0.000
Creatinine	0.93(0.91-1.01)	1.09(1.05-1.15)	1.11(1.03-1.17)	0.000
Urea	31(29-33)	34(30-38)	47(42-50)	0.000
FBG	119(114-122)	123(118-131)	138(131-147)	0.000
HbA1c	8.56(8.34-8.88)	9.76(9.28-10.04)	10.93(10.18-12.10)	0.000
eAG	198(192-208)	233(219-241)	267(230-300)	0.000

Data is presented as frequency and percentage or as median and interquartile range.
FBG: Fasting blood glucose, HBA1C: Glycated haemoglobin, eAG: Estimated average glucose.
p<0.05 was statically significant.

Table-9: Simple linear regression analysis of factors associated with plasma fibrinogen levels in patients with diabetic neuropathy.

Model	Unstandardised Coefficients		Standardised Coefficients	*t*-value	*p*-value	95% CI for B	
	B	Std. Error	correlation			Lower	Upper
Age (1-year)	0.427	1.547	0.036	0.276	0.783	-2.66	3.52
Gender (Male)	19.53	16.85	0.14	1.15	0.251	-14.17	53.24
Body mass index (BMI) kg/m^2	2.31	1.15	0.519	1.16	0.031	1.57	4.32
Blood pressure							
Diastolic pressure (1 mmhg)	3.03	1.11	0.278	2.71	0.009	.795	5.26
Systolic pressure (1 mmhg)	2.71	0.53	0.518	5.04	0.000	1.63	3.78
Diabetes duration (1-year)	-1.49	2.03	-0.09	-.73	0.466	-5.55	2.57
Medication used (Oral)	-10.76	16.91	-0.08	-.63	0.526	-44.59	23.06
Patients severity (1 point)	81.23	6.33	0.89	13.35	0.000	68.55	93.91
Sign symptoms							
Numbness, tingling, or burning sensation in the hands, feet, or legs (p)	98.67	17.27	0.69	5.71	0.000	64.11	133.22
Sharp or shooting pains (p)	107.36	11.70	0.76	9.17	0.000	83.94	130.77
Loss of sensation (p)	63.55	15.71	0.56	4.04	0.000	32.13	94.98
Muscle weakness or loss of coordination (p)	96.28	12.19	0.71	7.89	0.000	71.89	120.66
Digestive issues like bloating, constipation, or diarrhoea (p)	72.62	16.96	.53	4.28	0.000	38.69	106.59
Sexual dysfunction or decreased sexual response (p)	66.49	16.96	0.61	3.921	0.000	32.57	100.42
Biomarkers							
Creatinine (1 mg/dl)	361	88	0.63	4.10	0.000	183	539
Urea (1 mg/dl)	6.06	0.91	0.65	6.64	0.000	4.23	7.88
Fasting blood glucose (1 mg/dl)	3.14	0.58	0.67	5.40	0.000	1.98	4.31
HbA1c (1 %)	42.38	5.83	0.78	7.26	0.000	30.71	54.02
Estimated average glucose (1 mg/dl)	1.47	0.20	0.78	7.26	0.000	1.07	1.88

Dependent Variable: fibrinogen; P: Symptoms present, HbA1c: Glycated haemoglobin, CI: Confidence interval. P<0.05 was statically significant.

study may have reduced the generalisability of the findings. Future studies should be conducted with larger sample sizes and at multiple centres to validate the current findings. Third, the study did not evaluate patients with comorbidities. Fourth, most patients were elderly, which introduced a potential bias. The findings of the current study, as such, does not accurately represent the experiences and symptoms of younger individuals with diabetic MVCs.

Conclusion

The growth and progression of MVCs in T2DM patients was significantly influenced by plasma fibrinogen levels. Higher plasma fibrinogen levels were closely associated with an increased prevalence of MVCs. As such, fibrinogen may well act as a crucial biomarker for evaluating microvascular health.

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References

1. Nigussie K, Sertsu A, Ayana GM, Dessie Y, Bete T, Abdisa L, et al. Determinants of depression and anxiety among type 2 diabetes patients in governments' hospitals at Harari regional state, Eastern Ethiopia: A multi-center cross-sectional study. BMC Psychiatry 2023;23:13. doi: 10.1186/s12888-022-04494-x
2. Azeem S, Khan U, Liaquat A. The increasing rate of diabetes in Pakistan: A silent killer. Ann Med Surg (Lond) 2022;79:103901. doi: 10.1016/j.amsu.2022.103901
3. Petersmann A, Müller-Wieland D, Müller UA, Landgraf R, Nauck M, Freckmann G. et al. Definition, Classification and Diagnosis of Diabetes Mellitus. Exp Clin Endocrinol Diabetes 2019;127:S1-7. doi: 10.1055/a-1018-9078
4. Mufunda E, Tanyanyiwa VI. Diabetes: Implications for Health and Well-Being. In: Leal Filho W, Wall T, Azul A, Brandli L, Özuyar P, eds. Good Health and Well-Being, 1st ed. Series: Encyclopedia of the UN Sustainable Development Goals. Cham, Switzerland: Springer Nature Switzerland AG, 2020; pp 1-10. Doi: 10.1007/978-3-319-69627-0_128-1
5. Yan C, Chen J, Yang X, Li W, Mao R, Chen Z. Emerging Roles of Long Non-Coding RNAs in Diabetic Foot Ulcers. Diabetes Metab Syndr Obes 2021;14:2549-60. doi: 10.2147/DMSO.S310566
6. Srinivasan S, Singh P, Kulothungan V, Sharma T, Raman R. Relationship between triglyceride glucose index, retinopathy and nephropathy in Type 2 diabetes. Endocrinol Diabetes Metab 2020;4:e00151. doi: 10.1002/edm2.151
7. Patel HV, Sumple RS, Harshitha PK, Sumple KR. Association of plasma fibrinogen and development of complications in type 2 diabetes mellitus. Int J Res Med Sci 2023;11:1558-62. DOI: 10.18203/2320-6012.ijrms20231315

8. Francia GA, Pedraza C, Aceves M, Tovar-Arriaga S. Chaining a U-Net With a Residual U-Net for Retinal Blood Vessels Segmentation. IEEE Access 2020;8:38493-500. DOI: 10.1109/ACCESS.2020.2975745
9. Yılmaz Aydın F, Eynel E, Oruç İ, Ince H, Yüksel E, Aydın E. The Role of Monocyte to High-Density Lipoprotein Cholesterol Ratio in Predicting the Severity of Proteinuria and Renal Dysfunction in Primary Nephrotic Syndrome. Cureus 2021;13:e20345. doi: 10.7759/cureus.20345
10. Saxena S, Mathur A, Kakkar P. Critical role of mitochondrial dysfunction and impaired mitophagy in diabetic nephropathy. J Cell Physiol 2019;234:19223-36. doi: 10.1002/jcp.28712
11. Serdar CC, Cihan M, Yücel D, Serdar MA. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. Biochem Med (Zagreb) 2021;31:010502. doi: 10.11613/BM.2021.010502
12. American Academy of Ophthalmology (AAO). Diabetic Retinopathy Preferred Practice Pattern®. San Francisco, CA: 2019. [Online] 2019 [Cited 2023 May 05]. Available from URL: https://www.aao.org/education/preferred-practice-pattern/diabetic-retinopathy-ppp
13. National Eye Institute (NEI). Diabetic Retinopathy. [Online] [Cited 2023 May 05]. Available from URL: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy
14. American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43(Suppl 1):s135-51. doi: 10.2337/dc20-S011.
15. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline on Diabetes Mangement in Chronic Kidney Disease. [Online] 2019 [Cited 2023 May 05]. Available from URL: https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-Management-in-CKD_Public-Review.pdf
16. American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(Suppl 1):s151-67. doi: 10.2337/dc21-S011.
17. Dube S, Hulke SM, Wakode SL, Khadanga S, Thakare AE, Bharshankar RN, et al. Effectiveness of Semmes Weinstein 10 gm monofilament in diabetic peripheral neuropathy taking nerve conduction and autonomic function study as reference tests. J Family Med Prim Care 2022;11:6204-8. doi: 10.4103/jfmpc.jfmpc_195_22
18. Sekercioglu N, Lovblom LE, Bjornstad P, Lovshin JA, Lytvyn Y, Boulet G, et al. Risk factors for diabetic kidney disease in adults with longstanding type 1 diabetes: results from the Canadian Study of Longevity in Diabetes. Ren Fail 2019;41:427-33. doi: 10.1080/0886022X.2019.1614057
19. Hussein M, Menasri S. Prevalence of Microvascular Complications in Type 2 Diabetics Attending a Primary Healthcare Centre in Sudan. Int J Diabetes Metab 2019;25:127–33. Doi: 10.1159/000500914
20. Kasnakova P, Mihaylova A, Petleshkova P, Traykova N, Tornyova B. Purposeful physical activity-Basic strategy for the prophylaxis and treatment of diabetes and diabetic polyneuropathy. Biomed Res 2019;30:346-50.
21. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44(Suppl 1):s1-2. doi: 10.2337/dc21-Sint.
22. Wong TY, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. Nat Rev Dis Primers 2016;2:16012. doi: 10.1038/nrdp.2016.12
23. Fazili AB, Shah RJ, Mir MD, Jasmine A, Wani FA, Mushtaq B, et al. Ocular morbidity among diabetics attending the preventive ophthalmic clinic of a tertiary care institute with special reference to diabetic retinopathy. Int J Res Med Sci 2019;7:3722-9. DOI: 10.18203/2320-6012.ijrms20194299
24. Dhawale S, Jayant S, Gupta AK. Serum fibrinogen level in type 2 diabetes mellitus patients. Int J Adv Med 2016;3:83-7.
25. Bruno G, Cavallo-Perin P, Bargero G, Borra M, D'Errico N, Pagano G. Association of fibrinogen with glycemic control and albumin excretion rate in patients with non-insulin-dependent diabetes mellitus. Ann Intern Med 1996;125:653-7. doi: 10.7326/0003-4819-125-8-199610150-00005

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HU: Data collection, analysis, interpretation, study design, revision and drafting.
IA: Data collection, analysis, interpretation, study design, revision, drafting and final approval.
A: Data collection, analysis, interpretation, study design and drafting.
MA, MH: Data collection, revision and drafting.
ZU: Drafting and data collection.