(Investigate the effects of glycated hemoglobin (HbA1c) and plasma fibrinogen levels on the rheological properties of blood in people with type 2 diabetes mellitus)

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Abstract

Blood viscosity is a useful indicate for diagnosing and treating illnesses. It has been shown that individuals with Type 2 Diabetes Mellitus (T2DM) have higher blood viscosities, which may be a risk factor for cardiovascular problems, The effects of plasma fibrinogen and glycated hemoglobin (HbA1c) on the increased blood viscosity in T2DM patients under various chronic hyperglycemia circumstances are still unclear. Here, we assess how blood viscosity and HbA1c, together with plasma fibrinogen levels, relate to individuals with type 2 diabetes. The results of the research indicate that groups with higher HbA1c levels have a higher blood viscosity, however there does not appear to be a clear association between the two. In fact, we discover that there is a strong and positive correlation between the plasma fibrinogen level and the blood viscosity in T2DM people when we examine the impact of this level on blood viscosity. Additionally, to investigate how several variables (such as plasma fibrinogen levels and HbA1c levels) interact to modify blood

viscosity in type 2 diabetes, When we reassemble the experimental data using the T2DM blood viscosity values at both low and high shear rates, the findings show that the higher HbA1c level has very little effect on blood viscosity, Despite this, it is a significant measure of glycemic control in individuals with type 2 diabetes.Blood viscosity in type 2 diabetes is instead primarily determined by the increased blood hematocrit, the rapid red blood cell (RBC) aggregation caused on by the elevated plasma fibrinogen level, and the decreased RBC deformation. All of these experimental findings contribute to the understanding of the major factors that modify T2DM blood viscosity, and this knowledge can be applied to future research on the hemorheological abnormalities of T2DM patients.

Keywords: red blood cell, blood flow disturbances , blood viscosity, diabetes mellitus, low shear rate, high shear rate RBC aggregation, RBC deformation .

1. Introduction

The blood volume of an adult human is greater than five liters (6 quarts) on average. Blood transports nutrients and oxygen to live cells while eliminating waste from them . Additionally, it contains platelets that can patch a damaged blood artery to stop blood loss and distributes immune cells to combat infections.(1)

Because blood flow and artery walls severely stimulate blood cells mechanically during microcirculation, blood cells' mechanical and rheological characteristics are necessary for how well they carry out their biological functions. (6,7,8)

blood viscosity is an overall indicator of the intrinsic resistance to blood flow that is primarily determined by hematocrit, plasma viscosity, and erythrocyte deformation and aggregation. Therefore, the ability to measure blood flow and

tissue perfusion is essential for controlling blood rheological conditions, which produce resistance to fluid deformations (2).

Blood diseases are typically associated with an alteration in blood rheological properties,(9,10) and this Changes in blood viscosity (BV) and its rheological parameters have the potential to produce micro- and macrovascular damage, which can lead to significant cardiovascular events, as they are basic characteristics of blood viscosity and tissue perfusion.(2)

Thus, knowledge of blood's flow dynamics and rheological characteristics helps us recognize how blood viscosity affects cognitive processes and guides the development of therapeutic therapies.(10).

After much research on blood viscosity, it is now widely accepted that the rheological behavior of blood is largely influenced by five parameters: blood hematocrit (Hct), red blood cell (RBC) deformability, RBC aggregation, plasma viscosity, and temperature. (5,11)

Proteins like fibrinogen, a synthetic polymer, and plasma protein are responsible for the aggregation of red blood cells in blood flow, which encourage the generation of rouleaux-shaped RBC aggregates and ultimately raise blood viscosity (12,13).

The primary function of red blood cells is significantly influenced by their deformability, or their capacity to change shape in response to external force.(5)

Diabetes mellitus is a collection of physiological dysfunctions characterized by hyperglycemia caused directly by insulin resistance OR insufficient production of insulin. (3)

Diabetes can be caused by an abnormal insulin synthesis or secretion, such as Type I diabetes mellitus (T1 DM) and pancreatic duct stenosis, or by insulin resistance or subnormal production, such as Type 2 diabetes (T2 DM) and certain secondary diabetes. (4)

In general, blood glucose and glycated haemoglobin (HbA1c) levels are the most commonly used markers of glycemic management for diabetes patients.

The HbA1c level, which indicates the average glucose concentration over the eight to twelve-week period previously, is less biologically changeable than the previous one. (14)

Furthermore, the glycated serum protein (GSP) level—a measurement of glucose bound to total serum proteins—offers an alternative way to determine glycemia in circumstances when HbA1c may not be as helpful, such as pregnancy and shortened red blood cell longevity. The most common form of diabetes, type 2 diabetes mellitus (T2DM), is characterized by a relative insulin deficiencies caused on by pancreatic cell failure and insulin resistance in target organs. (15)

People with type 2 diabetes typically have higher HbA1c levels, which have been associated to an increasing risk of microvascular and macrovascular problems , such as diabetic retinopathy, diabetic nephropathy, diabetic peripheral and autonomic neuropathy. (16)

Blood viscosity is a direct indicator of blood's resistance to passing through blood vessels , Poiseuille's law indicates that the mathematical formula below can be used to determine the rate of blood flow through a small blood artery. (17)

$$Q = (\pi \times r^4 \times \Delta P) \,/\, (8 \times n_{BV} \times L)$$

When the blood viscosity is expressed as ηBV, the blood pressure differential between the blood vessel's ends is expressed as ΔP, and the blood's radius and length are expressed as r and L.

Increased blood viscosity, while holding other variables constant, prevents blood from passing through blood vessels, which exacerbates insulin resistance and type 2 diabetes (T2DM) and eventually results in diabetic microangiopathy and other circulation issues. (16)

2. Materials and Methods

2.1. Selection of T2DM Blood Samples

In this investigation, blood samples were obtained during fasting glucose testing from 318 T2DM patients (199 men and 119 women, mean age 56 ±12). To avoid the impact of postprandial lipid elevation on hemorheological features, patients undergoing fasting glucose testing were recommended to fast for the entire night prior to morning blood collection. (18)

Blood samples were taken at different HbA1c concentrations in order to investigate the impact of the HbA1c level on the hemorheological characteristics of T2DM blood, After 4 hours of blood withdrawal, all blood samples were taken and placed in a 5 mL vacuum tube with Heparin Lithium salt (75 IU/mL) anticoagulant, which was then refrigerated at 4 °C for in vitro testing. All 318 patients had testing for the two critical needs for evaluating long-term glucose management in diabetes: HbA1c and GSP levels.After blood centrifugation, the fraction of RBCs suspended in plasma was measured to estimate Hct values. Plasma fibrinogen (cFN) levels and other biochemical and hematologic indicators were assessed using standard protocols.

The whole blood viscosity was measured at native Hct using a cone-plate viscometer, Viscosity measurements were done within four hours after sample collection using these methods:

1- The force and gap required for the test were set as the rheometer's initialization, and the turntable and dosing pin were reset to 0.
2- The blood rheometer was heated to 37 degrees Celsius for 30 minutes.
3- Using a dosing needle for dilution (100:1), the whole blood was added to the tube and well combined.
4- The tube was placed on the pre-heated plate (37 degrees Celsius).
5- The two-dimensional curve for blood viscosity and shear rate was then determined in real time by the computer, which then automatically oversaw the full mensuration in a rapid, pointwise, prompt, steady-state way. Each sample took less than 30 seconds to complete the entire blood test.

Blood is a non-Newtonian fluid, which means its viscosity varies with shear rate, blood viscosity increases sharply at low shear rates due to RBC

aggregation , while at high shear rates, the blood becomes less viscous as the red blood cells separate, distort, and match in the direction of flow. 5

It's well knowledge that surface tension significantly influences the movement of liquids, It is often a surface characteristic of a liquid, created by forces acting out of balance on molecules at the surface that pull the liquid's bulk toward them, Thus, blood viscosity is a measurement of a liquid's resistance to change or transportation, and surface tension and viscosity are not significantly correlated.(19)

Therefore, we did not investigate how blood surface tension affected the blood viscosity values at low shear rates.

2.2. Statistical Analysis

All statistical data analyses were done by using SPSS 25.0 for Windows, the difference in investigated variables between groups with differing HbA1c and plasma fibrinogen levels was analyzed using one-way ANOVA and the Least Significant Difference (LSD) post-hoc test, Pearson's correlation analysis was performed to determine the statistical relationship between both continuous variables.

The independent relationship between clinical and biochemical factors and the levels of HbA1c and plasma fibrinogen was assessed using an easy correlation analysis.

A significance level of 0.05 was established for this experiment. A statistically significant relationship between at least two variables can be detected if the P-value is smaller than the significance level. The Pearson's correlation analysis also revealed the R-value and confidence interval (at a 95% confidence level).

3. Results and Discussion

3.1. Effect of Glycated Hemoglobin Level on T2DM Blood Rheology

Based on their HbA1c levels, patients with type 2 diabetes were divided into three groups: Group A had excellent glycemic control (HbA1c <6.5%), Group B had poor glycemic control (6.5 ≤ HbA1c < 10.0%), and Group C had the worst glycemic control (HbA1c > 10.0%).

Table 1 displays specific biochemical, hematologic, and hemorheological data for each of these three distinct groups. It reveals that persons with T2DM blood who have higher HbA1c levels (Groups B and C) had significantly higher GSP levels than individuals with lower HbA1c levels (Group A).

These three distinct groups have similar Hct levels; however, Groups B and C have higher RBC counts (N_{RBC}) than Group A, which results in lower MCV values in groups B and C according to the following equation:

$$MCV(fL) = \frac{Hct\%}{N_{RBC} \times 10^6 \mu L} \times 10$$

Table 1

Hematologic, hemorrhagic, and biochemical traits of the T2DM blood individuals sorted by HbA1c level tertile.

Item	individuals			P
	Group A	Group B	Group C	
Sex(M/F)	40/18	96/71	63/30	-
Age	56 ± 12	58 ± 12	56 ± 13	0.260
Hct (%)	42.03 ± 4.23	42.86 ± 4.24	42.33 ± 4.54	0.381
MCV (fL)	92.07 ± 4.84	91.44 ± 5.25	89.74 ± 3.57	0.005
N_{RBC} (10^6/μL)	4.58 ± 0.54	4.71 ± 0.58	4.73 ± 0.55	0.254
GSP (%)	2.00 ± 0.34	2.74 ± 0.63	3.92 ± 0.832	0.001
c_{FN} (mg/dL)	2.91 ± 0.43	3.07 ± 0.62	2.92 ± 0.65	0.079
η_{PV} (mPa·s)	1.38 ± 0.09	1.41 ± 0.09	1.41 ± 0.09	0.029
$\eta_{BV,\ 1}$ (mPa·s)	16.70 ± 3.26	17.06 ± 2.82	16.98 ± 3.08	0.739
$\eta_{BV,\ 50}$ (mPa·s)	4.45 ± 0.58	4.61 ± 0.60	4.57 ± 0.67	0.258
$\eta_{BV,\ 200}$ (mPa·s)	3.80 ± 0.48	3.91 ± 0.50	3.87 ± 0.56	0.395
Ai	4.38 ± 0.63	4.37 ± 0.57	4.40 ± 0.50	0.917
Ri	3.92 ± 0.61	3.98 ± 0.58	3.92 ± 0.67	0.687

HbA1c <6.5% in Group A, 6.5% ≤ HbA1c <10.0% in Group B, and HbA1c ≥ 10.0% in Group C. Hematocrit (Hct), mean cell volume (MCV), RBC count (NRBC), glycated serum protein (GSP), plasma fibrinogen level (pFN), and plasma viscosity (ηPV) Whole blood viscosity at shear rates η· = 1.0 s-1, 50.0 s-1, and 200.0 s-1 is represented by the values ηBV, 1.0, ηBV, 50.0, and 200.0; the RBC aggregation index is Ai, and the RBC rigidity index is Ri.

The plasma fibrinogen level cFN is somewhat greater in Group B than in the other two groups, but there are no significant differences between the three groups ($P = 0.079$). In addition, the RBC Ai and Ri levels are almost same in all three groups, suggesting that variations in the HbA1c level have little effect on these two parameters.

T2DM patients with high HbA1c levels (Groups B and C) have somewhat higher plasma viscosity (ηPV) compared to those with low HbA1c levels (Group A). Groups B and C had higher blood viscosity (ηBV) values at all three shear rates ($\gamma\cdot = 1$, 50, and 200 s-1) than Group A. There were no significant variations in mean ηBV values between the three groups ($P < 0.258$), showing that HbA1c level did not significantly affect blood viscosity.

3.2. Effect of Plasma Fibrinogen Level on T2DM Blood Rheology

The RBC aggregation caused by the plasma fibrinogen level in T2DM patients mostly determines the non-Newtonian flow characteristic of human blood, especially at low shear rates. It has been proposed that this behavior may be a risk factor for the onset and progression of diabetic microangiopathy.(20)

According to their plasma fibrinogen levels (cFN), all T2DM individuals are divided into three groups: Group A (cFN <2.5 mg/dL), Group B (cFN ≤ 3.5 mg/dL), and Group C (cFN > 3.5 mg/dL) in order to study the impact of cFN levels on blood viscosity in T2DM.

Table 2 shows the biochemical, hematologic, and hemorheological data of these blood subjects, The results demonstrate that at the three groups the mean Hct, MCV, RBC count, and HbA1c level do not differ statistically significantly ($P > 0.168$). In addition, it demonstrates that the RBC Ri is

unaffected by changes in plasma fibrinogen level cFN. In contrast, the data do demonstrate a stronger association between RBC Ai and plasma fibrinogen level cFN ($P = 0.035$), with greater values of RBC Ai in Groups B and C compared to Group A. These findings demonstrate that plasma fibrinogen primarily affects RBC aggregation properties. T2DM blood subjects with higher cFN (Groups B and C) have higher plasma viscosity (ηPV) and blood viscosity (ηBV) at all three shear rates ($\dot{\gamma} = 1$, 50, and 200 s-1), compared to those with lower cFN (Group A).

Table 2

the T2DM blood individuals' tertile of the plasma fibrinogen level (cFN), which indicates certain biochemical, hematologic, and hemorheological properties.

Item			individuals	P
	Group A	Group B	Group C	
Sex(M/F)	42/11	127/95	30/13	-
Age	55 ± 13	57 ± 12	59 ± 12	0.202
Hct (%)	42.22 ± 4.26	42.45 ± 4.34	43.54 ± 4.31	0.262
MCV (fL)	90.78 ± 4.31	91.26 ± 4.78	90.37 ± 5.56	0.491
N_{RBC} (10^6/μL)	4.66 ± 0.51	4.67 ± 0.57	4.84 ± 0.61	0.168
HbA_{1c} (%)	8.85 ± 2.49	8.68 ± 2.38	8.84 ± 2.49	0.857
η_{PV} (mPa·s)	1.37 ± 0.10	1.40 ± 0.09	1.45 ± 0.09	<0.001
$\eta_{BV, 1.0}$ (mPa·s)	15.94 ± 2.73	17.15 ± 2.97	17.32 ± 3.07	0.020
$\eta_{BV, 50.0}$ (mPa·s)	4.44 ± 0.63	4.57 ± 0.60	4.73 ± 0.68	0.064
$\eta_{BV, 200.0}$ (mPa·s)	3.78 ± 0.53	3.87 ± 0.49	4.04 ± 0.58	0.043
Ai	4.24 ± 0.52	4.43 ± 0.57	4.30 ± 0.53	0.035
Ri	4.01 ± 0.55	3.93 ± 0.62	3.99 ± 0.67	0.617

cFN <2.5 mg/dL in Group A; cFN ≤ 3.5 mg/dL in Group B; cFN > 3.5 mg/dL in Group C. The characteristics that have been picked and defined in this table are identical to those found in Table 1.

3.3. Multi-Factor Analysis in Altered T2DM Blood Rheology

Blood viscosity is affected by various causes, particularly in unhealthy conditions, Thus, the importance of the various biochemical, hematologic, and metabolic processes may be related to an elevated blood viscosity, It supplies

the basic mechanism of how these other variables transfer the pre-inflammatory damage to blood vessel walls.(21)

An additional approach to analysis is to classify patients according to the viscosity of their blood, In order to investigate the collective impact of various factors on modified blood rheology in type 2 diabetes, we are thinking about grouping the experimental data according to blood viscosity values at both low and high shear rates.(22)

Under low shear rate ($\gamma\cdot = 1.0$ s-1), blood viscosity values of all T2DM blood participants are separated into three groups: Group A (ηBV, 1.0 <15.0 mPa·s), Group B (15.0 mPa·s ≤ ηBV, 1.0 <19.0 mPa·s), and Group C (ηBV, 1.0 ≥ 19.0 mPa·s).

Table 3 shows selected biochemical, hematologic, and hemorheological data from these three blood groups. The results indicate that there are opposing trends in the Hct levels and RBC counts (NRBC) between Group A and Group C with age. This is compatible with previous research that found a decline in these two variables in older individuals.(23)

It also demonstrates that the mean values of HbA1c, GSP, and RBC Ri do not differ in a way that is statistically significant. In contrast to the results reported above, our findings reveal that the values of Hct, plasma fibrinogen level, cFN, and RBC Ai are gradually rising from Group A to Group C. the Low-density lipoprotein (LDL) cholesterol and plasma viscosity have been directly linked, according to a prior research by Irace et al. (2014). (24)

Here, we also take into account the average values of various cholesterol levels. Our findings reveal that the levels of LDL cholesterol raised from Group A to Group C, causing a gradual increase in plasma viscosity from Group A to Group C.

Table 3

T2DM blood subjects' biochemical, hematologic, and hemorheological features were assessed using a tertile of whole blood viscosity at a modest shear rate of $\gamma\cdot = 1.0$ s-1.

Item			individuals	*P*
	Group A	**Group B**	**Group C**	
Sex(M/F)	33/46	107/61	59/12	-
Age	63 ± 12	56 ± 12	54 ± 12	<0.001
Hct (%)	38.66 ± 3.06	42.90 ± 3.60	46.07 ± 3.68	<0.001
MCV (fL)	92.22 ± 5.03	90.90 ± 4.49	90.17 ± 5.11	0.027
N_{RBC} (10^6/μL)	4.20 ± 0.40	4.73 ± 0.45	5.13 ± 0.56	<0.001
c_{FN} (mg/dL)	2.92 ± 0.71	2.94 ± 0.53	3.23 ± 0.58	0.001
GSP (%)	3.01 ± 0.97	2.90 ± 0.94	3.07 ± 0.92	0.434
HbA_{1c} (%)	8.94 ± 2.43	8.70 ± 2.46	8.57 ± 2.27	0.621
HDL-C (mmol/L)	1.18 ± 0.32	1.22 ± 0.33	1.16 ± 0.27	0.445
LDL-C (mmol/L)	2.90 ± 0.92	3.16 ± 0.91	3.23 ± 0.97	0.060
TG (mmol/L)	1.46 ± 0.70	1.44 ± 0.87	1.65 ± 0.80	0.155
TC (mmol/L)	4.43 ± 1.23	4.70 ± 1.23	4.79 ± 1.24	0.163
η_{PV} (mPa·s)	1.39 ± 0.09	1.40 ± 0.10	1.43 ± 0.09	0.008
Ai	3.88 ± 0.40	4.42 ± 0.42	4.87 ± 0.54	<0.001
Ri	3.96 ± 0.64	3.97 ± 0.57	3.88 ± 0.69	0.583
$\eta_{rBV,\ low}$ (mPa·s)	29.63 ± 3.00	34.78 ± 2.80	40.36 ± 4.59	<0.001

1.0 <15.0 mPa•s for Group A; 15.0 mPa•s ≤ ηBV, 1.0 <19.0 mPa•s for Group B; 1.0 >19.0 mPa•s for Group C. The terms HDL-C and LDL-C refer to high and low density lipoprotein cholesterol, respectively; TG stands for triglyceride; TC stands for total cholesterol; and ηrBV means low blood viscosity at low shear rate. The definitions of the other parameters in this table match those in Tables 1 precisely.

Table 3 shows a significant rise in low ηrBV values from Group A to Group C. This is due to greater RBC aggregation (RBC Ai) caused by higher plasma fibrinogen levels.

All T2DM blood individuals are further classified into three groups based on blood viscosity values at high shear rate ($\gamma\cdot = 200.0$ s-1): Group A (ηBV, 200.0 <3.5 mPa·s), Group B (3.5 mPa·s ≤ ηBV, 200.0 <4.5 mPa·s), and Group C (ηBV, 200.0 > 4.5 mPa·s). Table 4 shows selected biochemical, hematologic, and hemorheological characteristics from these three groups. Identical to the results observed at low shear rates, It demonstrates that the values of MCV gradually drop from Group A to Group C, while the values of Hct, RBC count, and plasma fibrinogen level cFN gradually increase. Also, our findings indicate that the mean values of HbA1c and GSP do not differ in a way that is

statistically significant. On the other hand, we observe that while the values of the RBC Ai show minimal variation among the three groups, the RBC Ri values ascend gradually from Group A to Group C. We investigate the lowered blood viscosity at high shear rate (ηrBV, high).

Table 4 shows that the values of ηrBV gradually increase from Group A to Group C, which may be related to the lower RBC deformability, or increased RBC Ri.

Table 4

T2DM blood participants' biochemical, hematologic, and hemorheological features were analyzed by tertile of whole blood viscosity at a high shear rate of $\gamma\cdot$ = 200.0 s-1.

Item			individuals	*P*
	Group A	Group B	Group C	
Sex(M/F)	46/25	117/90	36/4	-
Age	63 ± 12	57 ± 12	50 ± 10	<0.001
Hct (%)	38.14 ± 2.70	43.06 ± 3.41	47.77 ± 3.62	<0.001
MCV (fL)	92.30 ± 5.27	90.88 ± 4.59	89.80 ± 4.73	0.021
N_{RBC} (10^6/μL)	4.15 ± 0.38	4.75 ± 0.46	5.34 ± 0.49	<0.001
c_{FN} (mg/dL)	2.91 ± 0.58	2.97 ± 0.57	3.29 ± 0.73	<0.01
GSP (%)	2.88 ± 1.03	2.98 ± 0.92	3.07 ± 0.91	0.590
HbA_{1c} (%)	8.91 ± 2.48	8.70 ± 2.42	8.56 ± 2.25	0.730
HDL-C (mmol/L)	1.16 ± 0.27	1.21 ± 0.34	1.14 ± 0.28	0.286
LDL-C (mmol/L)	2.89 ± 0.92	3.16 ± 0.91	3.31 ± 0.99	0.239
TG (mmol/L)	1.33 ± 0.67	1.46 ± 0.78	1.95 ± 1.05	0.036
TC (mmol/L)	4.36 ± 1.24	4.72 ± 1.21	4.85 ± 1.27	0.058
η_{PV} (mPa·s)	1.39 ± 0.10	1.40 ± 0.09	1.45 ± 0.09	<0.01
Ai	4.34 ± 0.70	4.40 ± 0.52	4.35 ± 0.49	0.658
Ri	3.41 ± 0.52	3.97 ± 0.47	4.67 ± 0.60	<0.001
$\eta_{rBV, high}$ (mPa·s)	4.70 ± 0.51	5.56 ± 0.53	6.73 ± 0.64	<0.001

A group has ηBV of 200.0 <3.5 mPa•s; B group has 3.5 mPa•s ≤ ηBV of 200.0 <4.5 mPa•s; C group has ηBV of 200.0 ≥ 4.5 mPa•s; ηrBV is high and reduces blood viscosity at high shear rate. Tables 1, 3 and this table's other specified parameters have the same definitions.

4. Summary

Blood viscosity is a direct indicator of blood resistance to flow, so,an increase in blood viscosity would cause blood flow to be slowed, which would lower the amount of nutrients like oxygen, insulin, and glucose that are transported to metabolically active tissues. In this work, we look at how the rheological characteristics of blood in individuals with type 2 diabetes mellitus (T2DM) are affected by the levels of plasma fibrinogen and glycated hemoglobin (HbA1c). Although the correlation between blood viscosity and HbA1c level is not clearly evident, our findings indicate that the mean values of blood viscosity are higher in groups with higher HbA1c levels, rather, the plasma fibrinogen level and the viscosity of blood in type 2 diabetes are found to be significantly and positively associated. Additionally, we regroup the experimental data based on the blood viscosity values at both low and high shear rates in order to evaluate the combined effects of numerous parameters (such as the HbA1c and plasma fibrinogen levels) on the changed blood viscosity in T2DM individuals. Although the high HbA1c level is a significant predictor of problems in individuals with type 2 diabetes, the experimental data indicate that its effect on blood viscosity is limited. Rather, the two most significant factors affecting the T2DM blood viscosity at low shear rates are increased blood hematocrit and enhanced RBC aggregation caused by the elevated plasma fibrinogen level, while the elevated T2DM blood viscosity at high shear rates is primarily caused by reduced RBC deformation and increased blood hematocrit. Overall, our research indicates that T2DM patients have increased RBC aggregation and lower RBC deformability, which may result in aberrant blood flow and ultimately vascular problems. One way that RBC hyperaggregability contributes to hemodynamic impairment and vascular occlusion is by increasing rouleau formation at low shear rates, which causes blood to become hyperviscous in capillaries and decreases the amount of nutrients that can reach metabolically active tissues, including glucose, insulin, and oxygen. Conversely, less cell deformation in RBCs from T2DM patients can also lead to an increase in blood viscosity, which impairs blood flow and contributes to other pathophysiological features of diabetes-related vascular problems such blood clot formation.