Journal of Diabetes Science and Technology
Volume 2, Issue 6, November 2008

REVIEW ARTICLE

Hemorheological Disorders in Diabetes Mellitus

Young I. Cho, Ph.D.,[1] Michael P. Mooney, B.S.,[2] and Daniel J. Cho, B.A.[2]

Abstract

The objective of the present study is to review hemorheological disorders in diabetes mellitus. Several key hemorheological parameters, such as whole blood viscosity, erythrocyte deformability, and aggregation, are examined in the context of elevated blood glucose level in diabetes. The erythrocyte deformability is reduced, whereas its aggregation increases, both of which make whole blood more viscous compared to healthy individuals. The present paper explains how the increased blood viscosity adversely affects the microcirculation in diabetes, leading to microangiopathy.

J Diabetes Sci Technol 2008;2(6):1130-1138

Introduction and Background

Diabetes mellitus is a syndrome characterized by disordered metabolism and abnormally high blood sugar (hyperglycemia) resulting from either low insulin level or insulin resistance at many body cells. Diabetes mellitus has high social and economic importance as the number of the diabetes patients continues to grow at an unprecedented rate throughout the world. Diabetes is the most frequent cause of legal blindness and renal failure and one of the major risk factors of cardiovascular diseases. Diabetes patients are five times more likely than nondiabetes patients to develop severe chronic leg ischemia, leading to foot ulceration and often, amputation.[1]

Hemorheological parameters in diabetes mellitus are often disturbed. These parameters include (but are not limited to) hematocrit, plasma proteins, erythrocyte aggregation, and erythrocyte deformability. The abnormalities associated with each of these parameters have been shown to markedly increase both plasma and whole blood viscosity (WBV). Whether or not blood viscosity determines blood flow resistance and microcirculation, and moreover, whether or not increases in viscosity can lead to the development of microvascular complications, are questions that should be subjected to further physiological and epidemiological studies. In addition, when the diameters of the capillaries of the eye and kidney are reduced in patients with diabetes because of the thickening of the basement membrane of capillaries,[2] the altered capillary structure increases flow resistance, leading to the impaired microcirculation. This resultant disturbance may be a risk factor for the progression of retinal failure in diabetic retinopathy and renal failure in diabetic nephropathy.

Author Affiliations: [1]Department of Mechanical Engineering and Mechanics, Drexel University, Philadelphia, Pennsylvania and [2]Rheologics Incorporated, Exton, Pennsylvania

Abbreviations: (RBC) red blood cell, (VRBC) volume of red blood cells, (WBV) whole blood viscosity

Keywords: hemorheological disorders, blood viscosity, erythrocyte deformability and aggregation, diabetes mellitus, microangiopathy

Corresponding Author: Young I. Cho, Ph.D., Department of Mechanical Engineering and Mechanics, Drexel University, 3141 Chestnut Street, Philadelphia, PA 19104; email address choyi@drexel.edu

Diabetes is also associated with an increased risk of atherosclerosis, which often occurs in elastic arteries of a diameter greater than 3 mm. The aforementioned hemorheological disturbance can amplify the micro-hemodynamic, particularly at the bifurcation. As a result, a significantly larger number of endothelial cells at the bifurcation become dysfunctional in diabetes patients compared to nondiabetes patients.

Erythrocyte Deformability

One of the hemorheological parameters altered in diabetes mellitus is the deformability of red blood cells (RBCs). Erythrocyte deformability was historically measured by the volume of RBCs (VRBC) filtered per minute through approximately 5 μm pore-size filters. The VRBC was found to be significantly reduced in diabetes patients compared with healthy controls. More recently, improved techniques for assessing RBC deformability, including laser diffraction techniques, have been utilized to address the clogging effects of white blood cells. Such methods have the ability to determine RBC deformability over a range of shear stresses.[3–6]

Red cells deform into an elliptical shape, aligning their long axis into the flow direction when blood moves at a relatively high velocity in a large arteries (i.e., greater than 3 mm in diameter) during systole. Even though 40–50% of the whole blood consists of red cells, they move almost like water drops in the large artery, posing a relatively small frictional penalty.

The erythrocyte deformability becomes more important in microcirculation. Guyton and Hall reported the minimum lumen of capillary vessels as 4–9 μm,[7] while other researchers have reported this diameter as 4–6, 4–8, and 5–7 μm.[8–11] What is noteworthy here is that because the size of red cells is typically approximately 8 μm, the deformability of the red cell can have a profound impact on microcirculation. It is crucial to perfusion for the red cells to pass through the capillaries in order to supply oxygen to the surrounding tissues. Additionally, it has been suggested that the impaired perfusion at the tissue level observed as a complication of diabetes mellitus is primarily due to the reduced erythrocyte deformability.[12,13]

The major determinants of the erythrocyte deformability include cell shape (i.e., the surface-to-volume ratio), mechanical properties of the cell membrane and its cytoskeleton, and intracellular viscosity, which is related to the mean cell hemoglobin concentration.[14,15]

Effects of Glucose on Erythrocyte Deformability

Diabetes mellitus is a disease associated with abnormal carbohydrate metabolism, arising from insulin deficiency and/or malfunction of insulin receptors, insulin being the key hormone in blood glucose homeostasis.[16] The consequent elevation of glucose in the blood plasma affects primarily RBCs and the vascular endothelial cells, including the walls of capillaries. The impaired glucose tolerance or uncontrolled blood glucose often results in microvascular complications of diabetes. An earlier study by Pirat[17] showed that as the degree of hyperglycemia increased, so did the incidence of complications, with the "poor" control group having the greatest incidence of retinopathy, nephropathy, and neuropathy.

Hyperglycemia is a crucial feature in diabetes. Abnormal glycation, which can adversely affect hemoglobin and membrane proteins in erythrocytes, has been shown to correlate with reduced membrane fluidity.[18] Separately, high values of glycosylated hemoglobin have been found to correlate with decreased deformability of erythrocytes.[19,20]

An elevated glucose level is traditionally associated with the insulin resistance syndrome or loss of insulin sensitivity. Pérez-Martin *et al*.[21] and other researchers[22–24] found that insulin sensitivity was negatively correlated to WBV. In other words, WBV is likely to mirror a host of various metabolic parameters controlled by insulin sensitivity (e.g., circulating lipids, glycemia, water and ion status, blood pressure, and obesity).[21] Whether or not improved glycemic control leads to beneficial rheological changes and further improves microcirculation is a noteworthy area for further investigation.

Erythrocyte Aggregation

If whole blood is allowed to sit *in vitro*, red cells begin to aggregate, a phenomenon which is known as Rouleaux formation. The erythrocyte aggregation also occurs *in vivo*. Whole blood stops briefly during diastole, particularly in a space between the aortic valve and aortic wall. Whole blood becomes briefly stagnant or recirculates at the bifurcations of a large artery. In addition, blood moves extremely slowly at the capillaries. For example, intensified RBC aggregation occurring in individual capillaries disturbs the normal blood flow inside their lumina and deranges the rheological properties of blood flow in the microvessels, which can slow to a full stop.[25,26] The RBC aggregates gradually grow larger

and become compressed, appearing homogeneous. This interferes with restoration of blood flow in capillaries.[26] Red cells continue to undergo the process of aggregation and disaggregation *in vivo* in the normal physiology.

Red blood cell aggregation occurs when the balance between aggregating and disaggregating forces breaks. The aggregating forces include the bridging forces due to adsorbed macromolecules such as fibrinogen on adjacent cell surfaces and the force produced by depletion-mediated effects with a preferential exclusion of macromolecules from the RBC surface that generates an osmotic gradient and fluid movement away from the intercellular gap and thus decreased cell-solvent affinity.[27] The disaggregating forces include fluid shear forces, electrostatic repulsion between cells, and the elastic energy of the cell membrane.[28,29] At the large arteries (e.g., coronary or carotid), the aggregating force may be greater than the disaggregating force except at the bifurcation, where the whole blood recirculates and becomes stagnant at the outer wall of the bifurcation due to the adverse pressure gradient. At this very location, erythrocytes in diabetes patients demonstrate increased adhesiveness to vascular endothelium,[30] amplifying the risk of atherosclerotic plaque development.

Red cells of patients with type 2 diabetes are known to aggregate more readily than those of normal subjects. In fact, the excessive aggregation of red cells is one of the most prominent features in patients with diabetes with poor glycemic control. The erythrocyte aggregation is an important hemorheological parameter because it directly affects WBV. Grigoleit and colleagues[31] considered abnormal rheological dynamics due to enhanced erythrocyte aggregation, the principal cause of vascular complications in diabetes mellitus since red cell aggregates cannot pass through the capillaries. More recent studies provide supporting data on the formation of red cell aggregates *in vivo*.[32–34] Furthermore, patients with type 2 diabetes exhibit a greater tendency than subjects without diabetes to develop peripheral vascular diseases in the lower extremities, and it has been suggested that enhanced erythrocyte aggregation contributes directly to this pathophysiology.[35–37]

Red cell aggregation is considered to be a primary cause of elevated WBV at low shear rates with respect to higher shear rates. For example, the WBV for a healthy person is approximately 20 cP at a low shear rate of 1 s^{-1} and approximately 4 cP at a high shear rate of 300 s^{-1}. The five-fold increase in the WBV observed at the low shear is attributed to the effect of red cell aggregation.

Whole Blood Viscosity

Whole blood is a suspension of plasma and cells. Because of the large quantity of cells, mostly erythrocytes, whole blood behaves as a non-Newtonian fluid, which means that blood is thicker at lower shear rates and becomes relatively thinner at higher shear rates. Blood viscosity at lower shear rates (e.g., at 1.0 s^{-1}) can be said to represent *in vivo* flow conditions corresponding to diastole, whereas the blood viscosity at the high shear rate (i.e., at 300 s^{-1}) can be said to represent *in vivo* flow conditions corresponding to the systole. There is a steady fall in viscosity as shear rates increase from low to high values. Shear rate is defined as a velocity gradient, which in actuality has a maximum value at the vessel wall and minimum value approaching zero at the center of the vessel. The low shear rate flow at the center of large vessels underscores the potential role of red cell aggregation in large vessels even at high blood flow rates.

Although hematocrit is one of the most important variables affecting the overall viscosity value of a given whole blood specimen, the magnitude of low shear viscosity is primarily determined by erythrocyte aggregation, whereas differences in high shear viscosity are robustly influenced by the erythrocyte deformability. Accordingly, low shear viscosity has a close correlation with the plasma fibrinogen and individual globulin concentrations. In general, blood viscosity depends both on macrorheological parameters, namely, hematocrit and serum proteins (fibrinogen and globulins), and on microrheological parameters, namely, the degree of RBC aggregation and deformability.

In macrovessels whose diameters are of the orders of magnitude larger than the size of red cells, blood viscosity plays a major role in determining flow resistance, assuming the vessel diameter remains constant. However, in the capillaries where the size of red cells is of the same order of magnitude as the lumen, the blood cannot be viewed to function as a uniform liquid, and the conceptual relevance of blood viscosity must be considered—especially as measured in the idiosyncratic geometries and flow regimes of rotational viscometers such as Brookfield or Contraves instruments, which are commonly used. In the microvessels, factors that would determine blood flow, such as hematocrit, RBC aggregation, RBC deformability, and plasma proteins, should be considered directly. This approach would be underscored by the fact that hematocrit in the microvessels is usually lower than in large vessels

and therefore lower than the hematocrits of specimens obtained by venipuncture and tested for viscosity *in vitro*.

Blood viscosity is a basic biological parameter that affects blood flow both at large arteries and in microcirculation. Abnormally high blood viscosity in unstable angina can play a role in further aggravating myocardial ischemia, because oxygen delivery is already diminished due to atherosclerotic plaque at the coronary artery. Additionally, increased WBV may increase injurious forces at the endothelial wall, thus adversely impacting endothelial function and thereby contributing to the inflammatory process.

In diabetes mellitus, there is sufficient evidence that the elevated blood viscosity is a pathogenetic factor of diabetic microangiopathy, altering microcirculation and leading to insufficient tissue nutrition.[31] In this regard, the increased blood viscosity manifests all the adverse microscopic alterations occurring in diverse structures of circulating blood in diabetes. Increased blood viscosity could be particularly important in the etiology of diabetic retinopathy.[38–40] Diabetic retinopathy can be described by dilated veins, microaneurysms, hemorrhages, and vessel proliferation. The etiology of the diabetic microangiopathy may be the impairment of the microcirculation leading to a prolonged reduction in the supply of oxygen and nutrients to the capillary vessels.[41–44] More specifically, the development of diabetic angiopathy has been related to abnormal hematocrit, plasma viscosity and erythrocyte aggregation,[45,46] and decreased erythrocyte deformability.[47,48] Since these parameters are the ones that determine the WBV, one may expect that the blood viscosity is also adversely altered in diabetic angiopathy.

A number of researchers found that the blood viscosity was altered in diabetes.[41,49,50] As the osmolarity of the blood increases due to increased sugar level, the capillary permeability increases, thus increasing hematocrit and subsequently the blood viscosity.[51] Lowe and coworkers[52] suggested that hyperglycemia may cause an osmotic diuresis and hence may lower plasma volume and increase hematocrit. Widespread increased microvascular permeability might lead to reduced plasma volume and hence increased hematocrit.[53] Increased hematocrit is associated with slowed retinal circulation. Barnes *et al*.[54] reported that both hematocrit and blood viscosity decreased after institution of good diabetic control. In summary, diabetes patients had higher blood viscosity than healthy people.[52,55]

Discussion

Skovborg *et al*. were the first to study blood viscosity in diabetes patients.[41] They found increased viscosity in 40 nonacidotic long-term diabetes patients as compared with 25 normal controls. The hematocrit-corrected blood viscosity measured with a Brookfield viscometer was 20% higher over a shear rate range of 1–10 s^{-1} in subjects with type 2 diabetes[41] and was significantly correlated with α2 and β globulins and fibrinogen concentration in subjects with type 2 diabetes.[56] **Table 1** gives the WBV for both control and diabetes mellitus at various shear rates as reported by a number of researchers. Here, we highlight some of these studies. The second column in **Table 1** indicates the number of subjects in the two groups: control subjects (C) and diabetic patients (P).

Le Devehat *et al*.[1] studied the hemorheology in diabetes patients without microangiopathy and macroangiopathy and showed an increased erythrocyte aggregation associated with an increased fibrinogen level while albumin levels were decreased. The hemorheological disturbances were found to be present even in diabetes patients without clinically detectable microangiopathy and/or microangiopathy. Paisey *et al*.[57] reported that hyperviscosity in diabetes was strongly related to hyperglycemia and influenced by the quality of diabetic control.

Barnes *et al*.[58] reported that blood viscosity at low shear rates was significantly higher in 64 patients with longstanding diabetes than in 61 matched nondiabetic controls. This increase was most striking in patients with either proliferative retinopathy or nephropathy, although it was present to a lesser extent in diabetes patients with evidence of myocardial or peripheral ischaemia. Erythrocyte deformability was lower in the 14 diabetes patients with the most extensive microangiopathy than in 22 diabetes patients with slight or no complications or in controls. They suggested that hyperviscosity and reduced erythrocyte deformability might well be important and potentially treatable factors in the etiology or progression of microcirculatory disease in diabetes.[58]

Cam *et al*.[59] studied the effects of hemorheological factors on the development of hypertension in children with diabetes without retinopathy and persistent microalbuminuria. Arterial blood pressures were measured in 46 children with diabetes and were compared with those of 29 healthy nonobese and 32 obese age- and sex-matched children. When compared with nonobese

Table 1.
Changes in Whole Blood Viscosity for Control Subjects and Patients with Diabetes Mellitus

Author	*N* (C/P)	Mean Hematocrit (C/P)	WBV (cP) Control	WBV (cP) Diabetics	Shear Rate (s^{-1})	Significance	Viscometry Instrument	Reference
Vekasi *et al.*	30/30	41.5/45.4	4.21 ± 0.04	5.01 ± 0.14	90	$p < .001$	Hevimet 40	64
Turchetti *et al.*	20/30	n/a	6.13 ± 0.98	7.71 ± 1.49	10	$p < .05$	CP Carri-Med	68
Schnyder *et al.*	24/17	45/45	36	32	0.1	n/a	Contraves 30	69
			5.0	5.2	94.5	$p < .05$		
Le Devehat *et al.*	32/76	41/39	4.27 ± 0.29	4.44 ± 0.57	128.5	n/a	Contraves 30	1
			12.15 ± 1.10	14.04 ± 3.11	1.75	$p < .01$		
Koscielny *et al.* (Type-I)	45/273	43/44	1	2.46	n/a		Capillary Microscopy	70
Zingg *et al.*	45/15	46/46	4.5 ± 0.5	4.6 ± 0.5	230	$p < .05$	Brookfield	71
			5.0 ± 0.5	5.1 ± 0.6	115	n.s.		
			6.0 ± 0.8	6.3 ± 0.8	46	$p < .05$		
			7.5 ± 1.0	8.3 ± 1.5	23	$p < .05$		
			9.1 ± 1.5	10.5 ± 1.6	11.5	$p < .05$		
Peduzzi *et al.*	30/30	42/41	4.78 ± 0.51	5.28 ± 0.82	225	$p < .01$	Brookfield	71
			5.57 ± 0.66	6.38 ± 0.99	90	$p < .01$		
			5.88 ± 0.82	6.92 ± 1.70	45	$p < .01$		
			6.98 ± 1.29	8.79 ± 3.04	22.5	$p < .01$		
Lowe *et al.*	38/18	45/47	6.75 ± 0.08	7.53 ± 0.17	100	$p < .01$	Contraves 30	52
	28/14	45/48	18.7 ± 0.06	24.3 ± 1.1	0.94	$p < .01$		
Linderkamp *et al.* (Type-I)	15/15	39/43	2.5 ± 0.5	3.0 ± 0.5	1000	$p < .05$	Capillary tube, 100 µm dia.	7
Skoborg *et al.*	16/16	36-49/36-49	4.327	4.943	230	$p < .02$	Brookfield	41
			4.744	5.217	115	$p < .001$		
			6.839	7.957	23	$p < .001$		
			8.285	9.991	11.5	$p < .001$		
			10.19	12.82	5.75	$p < .001$		
			13.17	16.48	2.30	$p < .001$		
			14.51	17.56	1.15	$p < .001$		
Violaris *et al.*	27/17	50/50	5.14 ± 0.39	5.39 ± 0.54	90	$p < .01$	Brookfield	73
			8.62 ± 1.06	9.77 ± 1.51	11.25	$p < .01$		
Rimmer *et al.*	23/34	43/44	4.31 ± 0.53	4.72 ± 0.56	230	n/a	Brookfield	74
Cam *et al.* (Type-I)	29/46	38/38	2.27 ± 0.4	2.55 ± 0.5	1000	$p < .05$	Harkness	59
Turczynski *et al.*	43/52	43.5F-47M	4.80 ± 0.37	5.30 ± 0.50	150	$p < .001$	Brookfield	75
Lo Presti *et al.*	30/19	44/43	3.43 ± 0.50	3.87 ± 0.49	450	$p < .01$	Brookfield	76
			3.70 ± 0.54	4.15 ± 0.51	225	$p < .01$		
			4.42 ± 0.78	4.82 ± 0.60	90	$p < .05$		
Ercan *et al.*	25/25	43/42	3.84 ± 0.81	5.13 ± 0.19	230	$p < .05$	Brookfield	77
			6.61 ± 1.91	11.73 ± 0.98	23	$p < .05$		

continued →

Table 1 continued

Author	*N* (C/P)	Mean Hematocrit (C/P)	WBV (cP) Control	WBV (cP) Diabetics	Shear Rate (s^{-1})	Significance	Viscometry Instrument	Reference
Marcinkowska-Gapinska and Kowal	20/18	44/44	3.50 ± 0.07	3.97 ± 0.94	100	n/a	Conraves LS40	78
			5.76 ± 0.20	6.90 ± 0.90	20	n/a		
			12.5 ± 0.60	13.7 ± 1.00	1	n/a		
Kaymaz *et al.*	10/10	n/a	3.8 ± 0.1	4.4 ± 0.2	300	$p < .001$	Brookfield	79
Barnes *et al.*	61/64	44.5/45	15.7 ± 0.2	17.4 ± 0.4	2.62	$p < .001$	Contraves LS100	58
			31.3 ± 0.5	36.4 ± 0.9	0.77	$p < .001$		

children, blood viscosity, plasma viscosity, serum viscosity, serum albumin, and plasma fibrinogen values were found elevated in diabetes patients and were correlated with systolic and diastolic blood pressure.

Lowe *et al*.[52] studied the role of blood viscosity and its major determinants (hematocrit, plasma fibrinogen, and plasma viscosity) in diabetes and diabetic retinopathy by studying young insulin-treated male diabetes patients with normal urea and creatinine levels who were otherwise healthy and on no medication. Diabetes patients without fundoscopic retinopathy ($n = 20$) had higher mean blood viscosity than controls at the high shear rate and the low shear rate. Lowe *et al*. showed that young male diabetics had increased blood viscosity at both high and low shear rates compared to nondiabetes patients and that this is present before the onset of clinically detectable retinopathy or other vascular complications. The increased viscosity was not due to an increase in hematocrit, for it persisted after correction for hematocrit differences between groups. They attributed the increased plasma viscosity to plasma fibrinogen.

The hemorheological disorders might promote stagnation of blood flow in the capillaries and postcapillary venules in diabetes patients. Circulatory stagnation is supposed to play an etiological role in capillary nonperfusion, in turn acting as a stimulus for new vessel formation, which represents a major cause of blindness in diabetes patients.[55] Increased viscosity reduces retinal blood flow, and the stagnation of blood flow in the microcirculation might result in local hypoxia, lactic acidosis, and hence microvascular damage.[60]

In an acute myocardial infarction for diabetes patients, the erythrocyte aggregates cannot pass through the capillaries,[31] thereby leading to the reduction of perfusion and eventual nonperfusion. Hence, reducing blood viscosity can increase blood flow in capillaries at the myocardium as well as other capillaries such as retinal vessels. Note that several researchers reported that retinopathies in nondiabetic hyperviscosity states, which are extreme cases with high levels of aggregation and plasma viscosity, were improved by lowering blood viscosity.[61–63]

Since increased RBC aggregation and increased low shear viscosity can impair microcirculatory flow, improved hemorheological factors via improved metabolic control may reduce microvascular complications of diabetes mellitus. Other methods of treatment to reduce hyperviscosity may include hemodilution, reduction of fibrinogen, plasmapheresis, or reduction of low-density lipoprotein.

Vekasi *et al*.[64] reported a pathologically raised plasma glucose concentration of the diabetes patients presenting at their outpatient unit, despite the fact that they had been on drug treatment for many years. They noted the fact that hyperglycemia that has existed for a long time could result in hemorheological disorders, leading to a disturbance in the microcirculation. These disturbances then cause ischemia at the different tissues,[65–67] which is the main reason for the formation of new capillaries, leading to retinopathy.

Grigoleit *et al*.[31] suggested the use of pharmaceutical agents capable of reducing blood viscosity for the treatment of vascular disorders in diabetes. They stated that since every diabetes patient can be considered a potential sufferer from vascular disease, and early lesions to terminal blood vessels have to be expected, improved tissue nutrition from increased capillary circulation as a result of reduced viscosity can acquire marked prophylactic relevance.

The data reviewed herein (see **Table 1**) make it very clear that generally patients with diabetes, both type 1

and type 2, have higher blood viscosity than controls. The differences at high shear rates are generally quite small at approximately 5%. At shear rates below 10 s^{-1}, however, the differences reach over 20%. The relatively strong consistency of this trend is noteworthy. However, the suggestion that such changes in blood viscosity can precipitate the major vascular complications associated with type 2 diabetes requires further study at the physiological level. The normal vasculature has the potential for a high degree of autoregulation, and viscosity may play a role in this autoregulation vis-à-vis wall shear stresses. The definition of shear wall stresses is the tangential frictional forces applied by blood flow against the endothelium of elastic arteries (with the exception of the cerebral arteries). Theoretically, the wall shear stress is a direct function of the blood viscosity and shear rate. As such, increased blood viscosity would directly affect the magnitude of wall shear stresses. Through a hemodynamic mechanism mediated by wall shear stresses, the elevated blood viscosity observed among type 2 diabetes patients, particularly in the low shear rate range, would be vasodilatory and, through vascular autoregulation, may stimulate a vasoconstriction response. Furthermore, preexisting or concomitant vascular pathologies that involve the loss of elasticity of the basal membrane of vessels in type 2 diabetes patients may limit shear-mediated vasodilation, amplifying the effects of disturbed viscosity in large arteries.

Conclusions

Diabetes mellitus is characterized by an elevated blood glucose level. The present paper reviewed the consequence of the elevated blood glucose level from a hemorheological point of view. The elevated glucose level stiffens the erythrocyte membrane, adversely altering the natural behavior of the erythrocytes, particularly in microcirculation. One of the most important consequences of altered erythrocytes is the elevated WBV. The WBV data reported by a number of researchers are tabulated for comparison. The present study found that the blood viscosity significantly increased in diabetes. The cause of the elevated blood viscosity is explained as the increased aggregation and reduced deformability of red cells. Furthermore, hematocrit was found to be elevated in diabetes due to increased permeability of capillary vessel wall, which in turn increases the WBV. The present paper concludes with the prevalence of hemorheological disorders in diabetes mellitus and recommends regular monitoring of the WBV, because this factor provides a panoramic view of various alterations that occur in erythrocytes.

Disclosures:

Young I. Cho is an advisor and consultant to Rheologics, Inc. Michael P. Mooney and Daniel J. Cho are employees of Rheologics, Inc. Rheologics, Inc. is a developer of a whole blood viscometer.

References:

1. Le Devehat C, Khodabandehlou T, Vimeux M. Impaired hemorheological properties in diabetic patients with lower limb arterial ischaemia. Clin Hemorheol Microcirc. 2001; 25(2): 43–8.
2. Barnes A, Willars E. "Diabetes" in Clinical Hemorheology. Chien S, Dormandy J, Ernst E, A Matrai A, eds. Dordrecht: Martinus Nijhoff; 1987, pp 275–309.
3. Ruef P, Pöschl JMB, Linderkamp O. The rheodyn SSD for measuring erythrocyte deformability. Biorheology. 1995;32(2):357–8.
4. Wang X, Zhao H, Zhuang FY, Stoltz JF. Measurement of erythrocyte deformability by two laser diffraction methods. Clin Hemorheol Microcirc. 1999;21(3-4):291–5.
5. Schauf B, Lang U, Stute P, Schneider S, Dietz K, Aydeniz B, Wallwiener D. Reduced red blood cell deformability, an indicator for high fetal or maternal risk, is found in preeclampsia and IUGR. Hypertens Pregnancy. 2002;21(2):147–60.
6. Shin S, Ku Y, Park MS, Jang JH, Suh JS. Rapid cell-deformability sensing system based on slit-flow laser diffractometry with decreasing pressure differential. Biosens Bioelectron. 2005;20:1291–7.
7. Guyton AC, Hall JE. Human Physiology and Mechanisms of Disease. 6th Ed. Philadelphia: W. B. Saunders; 1997.
8. Ross J Jr. "Cardiovascular system" in Best and Taylor's Physiological Basis of Medical Practice. 12th Ed. Baltimore: Williams & Wilkins; 1991.
9. Renkin EM. "Microcirculation and exchange" in Textbook of Physiology. 21st Ed. Patton HD, Fuchs AF, Hille B, Scher AM, Steiner R, eds. Philadelphia: W. B. Saunders; 1989, pp. 860–78.
10. Gaehtgens P. Flow of blood through narrow capillaries: rheological mechanisms determining capillary hematocrit and apparent viscosity. Biorheology. 1980;17(1-2):183–9.
11. Lipowsky HL, McKay CB, Seki J. "Trans time distributions of blood flow in the microcirculation" in Microvascular Mechanics: Hemodynamics of Systems and Pulmonary Microcirculation. Lee J, Skalak TC, eds. New York; Springer-Verlag; 1989, pp. 13–27.
12. Le Devehat C, Khodabandehlou T, Vimeux M. Relationship between hemorheological and microcirculatory abnormalities in diabetes mellitus. Diabete Metab. 1994;20(4):401–4.
13. Zimny S, Dessel F, Ehren M, Pfohl M, Schatz H. Early detection of microcirculatory impairment in diabetic patients with foot at risk. Diabetes Care. 2001;24(10):1810–4.
14. Stoltz JF, Singh M, Riha P. Hemorheology in Practice. Amsterdam: IOS ; 1999, pp. 27–50.
15. Chien S. Red cell deformability and its relevance to blood flow. Annu Rev Physiol. 1987;49:177–92.
16. Kumar V, Abbas A, Fausto N, eds. Robbins and Cotran Pathologic Basis of Disease. 7th Ed. Philadelphia: Elsevier Saunders; 2004.
17. Pirat J. Diabetes and its degenerative complications. A prospective study of 4440 patients observed between 1974 and 1973. Diabetes Care. 1978;1:168.
18. Watala C, Zawodniak M, Bryszewska M, Nowak S. Nonenzymatic protein glycosylation. I. Lowered erythrocyte membrane fluidity in juvenile diabetes. Ann Clin Res. 1985;17(6):327–30.
19. Bauersachs RM, Shaw SJ, Zeidler A, Meiselmann HJ. Red blood cell aggregation and blood viscoelasticity in poorly controlled type 2 diabetes mellitus. Clin Hemorheol. 1989;9:935–52.

20. Donner M, Siadat M, Stoltz JF. Erythrocyte aggregation: approach by light scattering determination. Biorheology. 1988;25(1-2):367–75.
21. Pérez-Martin A, Dumortier M, Pierrisnard E, Raynaud E, Mercier J, Brun JF. Multivariate analysis of relationships between insulin sensitivity and blood rheology: is plasma viscosity a marker of insulin resistance?. Clin Hemorheol Microcirc. 2001;25(3-4):91–103.
22. Brun JF, Dupuy-Fons C, Monnier JF, Micallef JP, Bouix D, Peyreigne C and Orsetti A. Blood viscosity is negatively correlated to insulin sensitivity. Biorheology. 1995;32:387–8.
23. Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE. Relationship between hemorheologic factors and insulin sensitivity in healthy young men. Metabolism. 1994;43(4):423–7.
24. Høieggen A, Fossum E, Moan A, Enger E, Kjeldsen SE. Whole-blood viscosity and the insulin-resistance syndrome. J Hypertens. 1998;16(2):203–10.
25. Robbins RC. Relation of blood cell aggregation to capillary resistance. Angiology. 1966;17:416–21.
26. McHedlishvili G, Varazashvili M, Gobejishvili L. Local RBC aggregation disturbing fluidity and causing stasis in microvessels. Clin Hemorheol Microcirc. 2002;26(2):99–106.
27. Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. Semin Thromb Hemost. 2003;29(5):435–50.
28. Chien S, Sung LA. Physiochemical basis and clinical implications of red cell aggregation. Clin Hemorheol Microcirc. 1987;7:71–91.
29. Meiselman HJ. Red blood cell role in RBC aggregation: 1963–1993 and beyond. Clin Hemorheol. 1993;13:575–92.
30. Wautier JL. Blood cell–vessel wall interactions. Clin Hemorheol Microcirc. 1992;12:55–8.
31. Grigoleit HG, Lehrach F, Muller R. Diabetic angiopathy and blood viscosity. Acta Diabet Lat. 1973;10:1311–24.
32. Kim S, Popel AS, Intaglietta M, Johnson PC. Effect of erythrocyte aggregation at normal human levels on functional capillary density in rat spinotrapezius muscle. Am J Physiol Heart Circ Physiol. 2006;290(3):H941–7.
33. Yalcin O, Uyuklu M, Armstrong JK, Meiselman HJ, Baskurt OK. Graded alterations of RBC aggregation influence *in vivo* blood flow resistance. Am J Physiol Heart Circ Physiol. 2004;287(6):H2644–50.
34. Sun C, Munn LL. Influence of erythrocyte aggregation on leukocyte margination in postcapillary expansions: a lattice Boltzmann analysis. Physica A. 2006;362(1):191–6.
35. Lowe GD. Blood rheology in arterial disease. Clin Sci (Lond). 1986;71(2):137–46.
36. Maser RE, Wolfson SK Jr, Ellis D, Stein EA, Drash AL, Becker DJ, Dorman JS, Orchard TJ. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: interrelations and risk factor profiles. Pittsburgh Epidemiology of Diabetes Complications Study-V. Arterioscler Thromb. 1991;11:958–65.
37. Osmundson PJ, O'Fallon WM, Zimmerman BR, Kazmier FJ, Langworthy AL, Palumbo PJ. Course of peripheral occlusive arterial disease in diabetes. Vascular laboratory assessment. Diabetes Care. 1990;13(2):143–52.
38. McMillan DE. Disturbance of serum viscosity in diabetes mellitus. J Clin Invest. 1974;53(4):1071–9.
39. Merimee TJ. Diabetic retinopathy. A synthesis of perspectives. N Engl J Med. 1990;322(14):978–83.
40. Williamson TH, Rumley A, Lowe GD. Blood viscosity, coagulation, and activated protein C resistance in central retinal vein occlusion: a population controlled study. Br J Ophthalmol. 1996;80(3):203–8.
41. Skovborg F, Nielsen AV, Schlichtkrull J, Ditzel J. Blood-viscosity in diabetic patients. Lancet. 1966;1(7429):129–31.
42. Cicco G, Pirrelli A. Red blood cell (RBC) deformability, RBC aggregability and tissue oxygenation in hypertension. Clin Hemorheol Microcirc. 1999;21(3-4):169–77.
43. Chmiel B, Cierpka L. Organ preservation solutions impair deformability of erythrocytes *in vitro*. Transplant Proc. 2003;35(6):2163–4.
44. Linderkamp O, Pöschl J, Ruef P. Blood cell deformation in neonates who have sepsis. NeoReviews. 2006;7:e517–23.
45. Schmidt-Schönbein H, Teitel P. *In vitro* assessment of "covertly" abnormal blood rheology: critical appraisal of presently available microrheological methodology. A review focusing on diabetic retinopathy as a possible consequence of rheological occlusion. Clin Hemorheol Microcirc. 1987;7:203–38.
46. Ziegler O, Guerci B, Muller S, Candiloros H, Méjean L, Donner M, Stoltz JF, Drouin P. Increased erythrocyte aggregation in insulin-dependent diabetes mellitus and its relationship to plasma factors: a multivariate analysis. Metabolism. 1994;43(9):1182–6.
47. Ernst E, Matrai A. Altered red and white blood cell rheology in type II diabetes. Diabetes. 1986;35(12):1412–5.
48. Vermes I, Steinmetz ET, Zeyen LJ, van der Veen EA. Rheological properties of white blood cells are changed in diabetic patients with microvascular complications. Diabetologia. 1987;30(6):434–6.
49. Dintenfass L. Blood viscosity factors in severe nondiabetic and diabetic retinopathy. Biorheology. 1977;14(4):151–7.
50. Schmid-Schönbein H, Volger E. Red-cell aggregation and red-cell deformability in diabetes. Diabetes. 1796;25(2 SUPPL):897–902.
51. Meiselman HJ, Merrill EW, Gilliland ER, Pelletier GA, Salzman EW. Influence of plasma osmolarity on the rheology of human blood. J Appl Physiol. 1967;22(4):772–81.
52. Lowe GD, Lowe JM, Drummond MM, Reith S, Belch JJ, Kesson CM, Wylie A, Foulds WS, Forbes CD, MacCuish AC, Manderson WG. Blood viscosity in young male diabetics with and without retinopathy. DiabetoIogia. 1980;18(5):359–63.
53. Langer L, Bergentz SE, Bjure J, Fagerberg SE. The effect of exercise on haematocrit, plasma volume and viscosity in diabetes mellitus. Diabetologia. 1971;7(1):29–33.
54. Barnes AJ, Locke P, Dormandy TL, Dormandy JA. Blood viscosity and metabolic control in diabetes mellitus. Clin Sci Mol Med. 1977;52:24–5.
55. Peduzzi M, Melli M, Fonda S, Codeluppi L, Guerrieri F. Comparative evaluation of blood viscosity in diabetic retinopathy. Int Ophthalmol. 1984;7(1):15–9.
56. Ditzel J. Haemorheological factors in the development of diabetic microangiopathy. Br J Ophthalmol. 1967;51(12):793–803.
57. Paisey RB, Harkness J, Hartog M, Chadwick T. The effect of improvement in diabetic control on plasma and whole blood viscosity. Diabetologia. 1980;19:345–9.
58. Barnes AJ, Locke P, Scudder PR, Dormandy TL, Dormandy JA, Slack J. Is hyperviscosity a treatable component of diabetic microcirculatory disease?. Lancet. 1977;2(8042):789–91.
59. Cam H, Püşüroğlu K, Aydin A, Ercan M. Effects of hemorheological factors on the development of hypertension in diabetic children. J Trop Pediatr. 2003;49(3):164–7.
60. Ashton N. Studies of the retinal capillaries in relation to diabetic and other retinopathies. Br J Ophthalmol. 1963;47:521–38.
61. Grindle CF, Buskard NA, Newman DL. Hyperviscosity retinopathy. A scientific approach to therapy. Trans Ophthalmol Soc UK. 1976;96(2):216–9.
62. Kopp WL, Beirne GJ, Burns RO. Hyperviscosity syndrome in multiple myeloma. Am J Med. 1967;43(1):141–6.

63. Schwab PJ, Okun E, Fahey JL. Reversal of retinopathy in Waldenstrom's macroglobulinemia by plasmapheresis. A report of two cases. Arch Ophthalmol. 1960;64:515–21.

64. Vekasi J, Marton ZS, Kesmarky G, Cser A, Russai R, Horvath B. Hemorheological alterations in patients with diabetic retinopathy. Clin Hemorheol Microcirc. 2001;24(1):59–64.

65. Chien S. Hemorheology in clinical medicine. Clin Hemorheol. 1982;2:137–42.

66. Kesmarky G, Toth K, Habon L, Vajda G, Juricskay I. Hemorheological parameters in coronary artery disease. Clin Hemorheol Microcirc. 1998;18(4):245–51.

67. Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, Elwood PC. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. Circulation. 1991;83(3):836–44.

68. Turchetti V, Leoncini F, De Matteis C, Trabalzini L, Guerrini M, Forconi S. Evaluation of erythrocyte morphology as deformability index in patients suffering from vascular diseases, with or without diabetes mellitus: correlation with blood viscosity and intra-erythrocytic calcium. Clin Hemorheol Microcirc. 1998;18(2-3):141–9.

69. Schnyder L, Walter R, Rohrer A, Contesse J, Reinhart WH. No influence of C-peptide, insulin, and glucagon on blood viscosity *in vitro* in healthy humans and patients with diabetes mellitus. Clin Hemorheol Microcirc. 2001;24(2):65–74.

70. Koscielny J, Latza R, Wolf S, Kiesewetter H, Jung F. Early rheological and microcirculatory changes in children with type I diabetes mellitus. Clin Hemorheol Microcirc. 1998;19(2):139–50.

71. Zingg W, Sulev JC, Morgan CD, Ehrlich RM. Blood viscosity in diabetic children. Diabetologia. 1971;7(6):461–2.

72. Linderkamp O, Ruef P, Zilow EP, Hoffmann GF. Impaired deformability of erythrocytes and neutrophils in children with newly diagnosed insulin-dependent diabetes mellitus. Diabetologia. 1999;42(7):865–9.

73. Violaris K, Bitzos E, Rudolph N. Increased blood viscosity and tachypnoea in infants of diabetic mothers. Arch Dis Child. 1986;61(9):910–2.

74. Rimmer T, Fleming J, Kohner EM. Hypoxic viscosity and diabetic retinopathy. Br J Ophthalmol. 1990;74(7):400–4.

75. Turczyński B, Michalska-Małecka K, Słowińska L, Szczesny S, Romaniuk W. Correlations between the severity of retinopathy in diabetic patients and whole blood and plasma viscosity. Clin Hemorheol Microcirc. 2003;29(2):129–37.

76. Lo Presti R, Sinagra D, Montana M, Scarpitta AM, Catania A, Caimi G. Haemorheological profile in metabolic syndrome. Clin Hemorheol Microcirc. 2002;26(4):241–7.

77. Ercan M, Konukoğlu D, Erdem T, Onen S. The effects of cholesterol levels on hemorheological parameters in diabetic patients. Clin Hemorheol Microcirc. 2002;26(4):257–63.

78. Marcinkowska-Gapińska A, Kowal P. Blood fluidity and thermography in patients with diabetes mellitus and coronary artery disease in comparison to healthy subjects. Clin Hemorheol Microcirc. 2006;35(4):473–9.

79. Kaymaz AA, Tamer S, Albeniz I, Cefle K, Palanduz S, Ozturk S, Salmayenli N. Alterations in rheological properties and erythrocyte membrane proteins in cats with diabetes mellitus. Clin Hemorheol Microcirc. 2005;33(2):81–8.