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Whole-blood viscosity and metabolic syndrome

Whole-blood viscosity (WBV) depends on vascular geometry and blood physiological constituents. Diabetes mellitus, hypertension, dyslipidemia and obesity — the major components of metabolic syndrome (MetS) — can independently affect blood vessels and microcirculation. MetS is the state of oxidative stress and systemic inflammation. Pro-oxidant and inflammatory cytokines induce endothelial dysfunction. Morphological alterations of erythrocytes could be a consequence of decreased erythrocytes deformability, oxidative stress and systemic inflammation. These events altogether lead to increased WBV. In this review, the effect of WBV in different components of the MetS and WBV with regard to oxidative stress and inflammation — common states in chronic disease — are discussed.

**KEYWORDS:** diabetes mellitus • hypertension • metabolic syndrome • obesity • whole-blood viscosity

Blood viscosity is the intrinsic resistance to blood flow developed due to the frictional force between adjacent layers of flowing blood. Blood is a non-Newtonian fluid and its viscosity depends on the shear rate. According to the Poiseuille equation, rate of blood flow depends on the pressure difference between the ends of the vessels, as well as the blood vessel’s radius and length, and the viscosity of blood. As the diameter of the capillary is reduced (below 0.3 mm), the whole-blood viscosity (WBV) is reduced and Poiseuille’s law is not valid [1]. Abnormalities that cluster in metabolic syndrome (MetS) are likely to impair the blood vessels, endothelium and blood rheology [2]. Kahn *et al.* have stated that no single underlying pathological process can be attributed to the state of MetS [3]. They further argued that the criteria for defining MetS are ambiguous and incomplete. In this review, the changes in WBV in different components of MetS are focused upon (i.e., diabetes mellitus [DM], hypertension, obesity and dyslipidemia), and the WBV with regard to oxidative stress — a common state in chronic disease is also discussed [4].

**DM & WBV**

In an Atherosclerosis Risk in Communities study involving 12,881 patients, WBV calculated according to a validated mathematical formula (estimated WBV) at shear rate of 208 s⁻¹ was found to be positively correlated with high BMI, waist circumference (WC), waist:hip ratio, systolic blood pressure, fasting plasma glucose level, serum insulin level, plasma fibrinogen level, white blood cell count and serum triglyceride (TG) levels, and it was inversely associated with serum HDL cholesterol (HDLc) levels. DM was positively associated with WBV, rising from 11.2 per 1000 person-years in the lowest quartile of blood viscosity to 20 per 1000 person-years in the highest quartile. This almost twofold gradient persisted after adjustment for age, sex and race. After simultaneous adjustment for age, sex, race, parental history of DM, education, field center, BMI, waist:hip ratio, smoking and physical activity, risk for the incidence of Type 2 DM was still strongly associated with elevated WBV [5]. This large community-based study strongly suggests that WBV is associated with insulin resistance and is the independent predictor of Type 2 DM. In another study, insulin sensitivity of healthy young men was determined by the hyperinsulinemic isoglycemic glucose clamp technique and was correlated with WBV measured by the Bohlin CS 10 rheometer (Bohlin Instruments Ltd, Lund, Sweden). Statistically significant negative correlation was found between the glucose disposal rate and WBV at both high (201 s⁻¹) and low (0.5 s⁻¹) shear rate [6]. WBV was highest at the lowest quartiles of insulin sensitivity and there was
a trend to increase WBV progressively across decreasing quartile of insulin sensitivity [7]. The rate of blood flow in skeletal muscle is affected by the concentration of insulin in blood [8]. Insulin vasodilates skeletal muscle vasculature via an endothelium-derived nitric oxide-dependent mechanism [9]. Insulin-mediated increase in muscle perfusion accounts for approximately 30% of insulin’s overall action to stimulate muscle glucose uptake [10]. It was demonstrated that an 8-h infusion of intralipid and heparin reduced the effect of insulin on blood flow by approximately 50%. There exists an insulin concentration gradient between blood and interstitial fluid and the glucose disposal rate from blood depends on insulin concentration in interstitial fluid [11].

Steinberg et al. showed that prolonged elevation of systemic free fatty acid (FFA) levels induced impairment of insulin-mediated vasodilation in normotensive lean insulin-sensitive subjects [12]. Hyperlipidemia in vivo may reduce glucose uptake by lowering blood flow in insulin-sensitive tissues [12,13]. Glucose delivery to skeletal muscle is reduced due to reduction in the blood flow [6]. Similarly, reduction in the blood flow also limits the ability of insulin to reach its effective concentration in its receptors. [10, 14]. FFA-mediated reduction in blood flow could be attributed to its hemorheological effect. Excess FFAs are responsible for erythrocyte crenation [15]. It was demonstrated by light microscopy that the erythrocytes from healthy subjects changed their shape from biconcave to highly transformed forms such as monoconcave forms and ‘shrunken cells’ after incubation with FFA palmitate (0.2 mM) for 15 min. At a higher concentration of palmamate, cell swelling and even ghost formation was observed [16]. Excess FFAs alter the morphology of erythrocytes and decrease their deformability [17] and, thus, increase WBV. Elevated WBV then causes reduction of insulin delivery in the skeletal muscle and as a result, insulin mediated vasodilation is reduced. Hence, elevated WBV could be another link between FFA toxicity and insulin resistance.

Glucose oxidation and protein glycation, caused by diabetes-associated hyperglycemia, may induce modifications in the mechanical and rheological properties of erythrocytes. To demonstrate the effect of glucose on erythrocyte deformability, erythrocytes from ten healthy volunteers were incubated in vitro for a maximum of 2 h with an increasing concentration of glucose. Deformability characteristics were reduced when compared with erythrocytes incubated in glucose-free media [18]. Erythrocyte deformability was also found to be correlated with glycated hemoglobin (HbA1c) among 45 Type 2 diabetic patients with normal cholesterol levels and without any cardiovascular complications [19]. The membrane protein glycation, in part, may determine the structural alterations in erythrocytes, their reduced deformability and, consequently, increased WBV [20]. To investigate the in vivo effect of glucose concentration on the hemorheology, Koltai et al. divided 30 patients into two groups according to their glucose tolerance status: 14 with impaired glucose tolerance (IGT) or DM, and 16 with normal glucose tolerance [21]. Erythrocyte aggregation was higher at the second and third hour; plasma viscosity was higher at the first and second hour and WBV, measured in a Hevimet 40 (Hemorex Ltd, Hungary) capillary viscometer, was higher only at the first hour after glucose intake in the IGT or diabetic group in comparison with the normal group. No significant difference was noted between the two groups in erythrocyte filterability during the study period. The observation of a lack of change in erythrocyte deformability throughout the time course and the elevated WBV only at the first hour after glucose intake in the IGT group suggests that glucose toxicity due to hyperglycemia in vivo may be a reason for elevated WBV. Other studies have reported hematocrit (Hct), fibrinogen and erythrocyte aggregation to be higher in patients with Type 1 DM, and a low shear rate WBV and elevated fibrinogen can be found in patients with Type 2 DM in comparison with nondiabetics [22]. HbA1c was significantly correlated with fibrinogen, erythrocyte aggregation and low shear rate blood viscosity in patients with Type 1 DM, and with fibrinogen and erythrocyte aggregation in patients with Type 2 DM [22].

Absolute WBV measured by a cone-plate viscometer at a shear rate of 150 s⁻¹, plasma viscosity and 45% Hct standardized WBV was found to be higher in diabetic retinopathy subjects in comparison with normal controls, and retinopathic severity was positively correlated with whole blood and plasma viscosity [23]. Indeed, it is known that increased blood viscosity exists in patients who have retinal vein occlusion and also that diabetes with retinopathy comorbidity is associated with a higher level of blood viscosity compared with diabetes without retinopathy [24].
By contrast, elevated WBV has been shown to have a positive impact on diabetic retinopathy [25]. Estimated WBV and Hct were higher in diabetic subjects without retinopathy in comparison with diabetic subjects with retinopathy.

**Hypertension & WBV**

Conflicting association between low shear rate WBV and cardiovascular events has been reported, especially in subjects with essential hypertension without history of cardiovascular disease (CVD), DM and renal disease. In one study, low shear rate WBV measured in a rotational viscometer was positively correlated with both systolic and diastolic blood pressure [26]. The same study also showed that essential hypertensive patients at the highest tertile of low shear rate WBV had a higher BMI, were frequently smokers and had higher TG levels and a low HDLc concentration [26]. By contrast, a study by Devereux et al. reported that although the differences in WBV between hypertensive and normotensive subjects were significant at the high shear rates of 450, 225 and 90 s⁻¹, the difference at the low shear rate of 45 s⁻¹ was not significant [27]. In the Edinburgh Artery Study (a prospective study of a random population sample), WBV measured in a Coulter–Harkness viscometer was shown to be associated with cardiovascular complications (ischemic heart disease and stroke). The relative risk of cardiovascular events due to elevated WBV was as strong as established risk factors, such as increased LDL cholesterol (LDLc) and high blood pressure. Plasma viscosity and fibrinogen levels were also shown to be associated with CVD [28]. Letcher and colleagues measured blood and plasma viscosity in 49 untreated patients with essential hypertension and an equal number of normal controls, and reported that the blood viscosity measured at six different shear rates was significantly correlated with blood pressure, and WBV was also higher in hypertensive subjects [29]. These authors also noted that when the Hct-matched hypertensive subgroup was compared with controls, WBV was still higher in patients with essential hypertension. Since the viscosity of defibrinated blood was similar in normal and hypertensive subjects with matched Hct; high fibrinogen level was suggested as one of the main factors for elevated WBV in hypertension. However, the lack of correlation of fibrinogen with plasma viscosity and erythrocyte aggregation in hypertensive cases has also been reported [30]. In the same study, WBV was found to be higher in the hypertensive group even after correction for Hct. Therefore, the authors concluded that, apart from fibrinogen levels and hemoconcentration, other factors (e.g., proteins such as albumin and hemorheological factors) may play role in increasing WBV in essential hypertension.

Plasma volume is decreased in hypertension due to increased filtration pressure and this leads to increased hemoconcentration and, hence, elevated WBV [31,32]. Increased adrenergic sympathetic system activity may also be a cause for decreased plasma volume and hence increased WBV [30]. Puniyani and coworkers studied hemorheological profiles in 37 patients with hypertension, 48 patients with coronary heart disease and 36 patients with a history of myocardial infarction [33]. A significant increase in WBV (measured in a cone plate viscometer) was reported in subjects with hypertension, history of myocardial infarction and hypertension followed by ischemic heart diseases when compared to controls. In the case of ischemic heart disease, no significant change in WBV was reported, although plasma viscosity was elevated and erythrocyte deformability was reduced. The authors suggested that an alteration of blood rheology imposes greater risk of CVD through changes in central and peripheral hemodynamics.

**Dyslipidemia & WBV**

Several studies have associated increased WBV or plasma viscosity with dyslipidemia [34–40]. Absolute and Hct-corrected WBV was positively correlated with total cholesterol (TC), TG and LDLc, and was negatively correlated with HDLc [6,41–43]. Hypertriglyceridemia and hypercholesterolemia increase the plasma viscosity due to elevated lipoprotein concentration [44]. LDL may also enhance the interaction or aggregation among erythrocytes, thereby leading to increased WBV [41,45]. High levels of TC and LDLc may favor the oxidation of erythrocyte membrane lipids [39]. In the study by Aloulou et al., 90 subjects were classified into four groups based on the guidelines from the 2001 National Cholesterol Education Program Adult Treatment Panel III [42]. No significant changes in blood rheology across classes of National Cholesterol Education Program score were found, but WBV was negatively correlated with HDLc and positively correlated with TG. The authors suggested that the effect of obesity and insulin resistance on hemorheology may be indirectly through dyslipidemia. It has been demonstrated that erythrocyte permeability
in vivo is impaired by high levels of TC and LDLc [46]. HDL inhibits Ca²⁺-induced procoagulant activity on erythrocyte membranes [47]. HDL also competes with LDL for binding with the erythrocyte membrane, competitively inhibiting LDL-induced erythrocyte aggregation, thus decreasing WBV [48].

Low shear rate WBV measured in a rotational viscometer was reported to be higher in patients with familial hypercholesterolemia (FH). Although there was no significant difference in Hct level between the FH group and normal lipid profile group, red blood cell aggregation and plasma viscosity were higher in the former [49]. The effect of cholesterol-lowering treatment on hemorheology was also studied in the same FH group. Pravastatin and cholestyramine significantly reduced the concentration of serum TC and LDLc in FH patients after 12 weeks. Fibrinogen concentration and plasma viscosity were reduced after 12 weeks by pravastatin, but not by cholestyramine. No significant reduction of WBV at both high and low shear rate was found after treatment with either of the two drugs. Similarly, in the study by Sola et al., 41 subjects with severe or morbid obesity without any other CVD risk factors, such as hypertension, DM and dyslipidemia, were kept on a very low caloric diet for a month [50]. A significant decrease in serum LDLc, HDLc, TG and TC was noted along with reduced BMI after intervention. In spite of the decrease in lipid parameters and BMI, there was no decrease in fibrinogen level, Hct, WBV and plasma viscosity. If the effect of lipoprotein on blood viscosity is attributed to its high-molecular-weight effect, then the effect of LDLc and HDLc on viscosity should have been the same. If it was not the same owing to low molecular weight and low concentration of HDLc in the plasma compared with LDLc, then the effect should at least be in the same direction; however, this was not the case. WBV has been correlated negatively with HDLc [41,48,51,52] and positively with LDLc [41,48]. Although an abnormal lipid profile has adverse effects on WBV, the association is not direct and depends on the complex interaction of dyslipidemia with other biochemical and metabolic factors.

**Obesity & WBV**

Obesity is the central and causal component of MetS [53]. In a Strong Heart Study, hypertensive patients who were not under antihypertensive medications, did not have any overt cardiovascular complications and had only mild elevation of blood pressure, were recruited along with obese and diabetic cases [54]. Estimated WBV was found to be higher in obese cases compared with nonobese cases [54]. In another study, 24 obese subjects did not show significant change in WBV at a high shear rate (94.5 s⁻¹), either at absolute value or corrected at standard Hct of 45% after 20-kg weight loss [55]. Although Hct and fibrinogen levels were high after 20-kg weight loss, the differences were statistically insignificant. WBV at a low shear rate (0.2 s⁻¹) showed no change at absolute value, but when corrected for standard Hct, it was significantly reduced after slimming [55]. Reduction in low-shear-rate, Hct-corrected WBV in obese subjects cannot be attributed to fibrinogen and no association between metabolic and hemorheological parameters was shown in the study. Improvement in blood fluidity at low shear rate of obese subjects could be due to complex biochemical and endocrine changes after weight loss. Such changes could suggest reduced blood aggregation and improvement in insulin resistance. On the other hand, Zhu et al. have shown a higher high shear rate WBV (200, 30 and 5 s⁻¹) in obese children compared with age- and height-matched nonobese children, but there was no difference in low shear rate WBV (1 s⁻¹) and the erythrocyte aggregation index [56]. The authors also showed that WBV measured at a higher shear rate was a strong predictor of endothelial dysfunction. In addition, increased WBV was shown in 90 obese subjects with established CVDs at low and high shear rates compared with age- and sex-matched controls, and WBV at both shear rates was correlated significantly with BMI [57].

WBV and Hct were reported to be higher in obese men compared with obese women, but there was no difference in the Hct-corrected WBV level [58]. The erythrocyte aggregation index was positively correlated with WBV in both obese men and women. Elevated Hct, as well as the tendency of erythrocytes to aggregate in obese patients, could be considered as main factors, among others, for increased WBV. Erythrocyte fluidity was found to be decreased in morbidly obese women [59]. Altered erythrocyte deformability and aggregation found in obese patients [58–60] could have an adverse influence on WBV. WBV at a high shear rate is influenced by erythrocyte deformability [20]. In a study involving 109 Japanese obese patients (BMI ≥25), it was shown that blood passage time (BPT) through a siliconized microchannel array
was significantly higher in the MetS group than in the non-MetS obese groups [61]. In addition, BPT correlated with the severity of MetS (assessed by the number of positive components). BPT was also significantly correlated with MetS variables, such as increases in body weight, BMI, WC, systolic blood pressure, diastolic blood pressure and serum TG level [61]. The authors also investigated the effects of weight reduction on BPT and showed that BPT significantly decreased in patients with weight reduction of greater than 3%. The decrease of BPT by weight reduction was significantly related with the reduction of WC and systolic blood pressure. The results suggest that various components of MetS and mostly central obesity contribute to decreased erythrocyte deformability. By contrast, in another study involving obese cases without other concomitant cardiovascular risk factors, erythrocyte deformability was not found to be reduced [62]. Nevertheless, obese patients with MetS showed lower erythrocyte deformability than obese patients without MetS and, hence, it was concluded that insulin resistance, and not obesity, was responsible for lower deformability [62]. Plasma fibrinogen level, plasma viscosity and low shear rate WBV were reported to be high in obese adolescents without other metabolic complications [63]. These obese adolescents with the same Hct level as those of controls were kept on a balanced diet for 1 month and hemorheological parameters were further tested. Plasma viscosity, plasma fibrinogen level and the mean erythrocyte aggregation index decreased significantly, while there was no change in WBV. Serum TC level and BMI were also significantly reduced. Decreased fibrinogen and possible metabolic rearrangement could account for improvement of certain rheological parameters, such as plasma viscosity and erythrocyte aggregation after dieting. Lack of change in WBV suggests that association of blood rheology with obesity is not simple and direct. No significant hemorheological improvement after weight loss has been reported by other authors [64–66]. We propose that adipokines [67,68], such as IL-6 [69], TNF-α [70], plasminogen activator inhibitor-1 [71] and proteins of the renin–angiotensin system [72] secreted from adipose tissue, may alter the hemorheology through complex metabolic, endocrine and genetic interactions.

**Oxidative stress & WBV**

Erythrocytes play a significant role in scavenging free radicals [73–75] and it was proposed that in carrying out this role, erythrocytes become damaged by oxidation, which consumes endogenous reducing substances [76]. In a study by Richards and Nwose, 154 subjects were categorized into four groups: controls, pre-DM, DM and DM with CVD complications [77]. WBV in these subjects was associated with erythrocyte oxidative stress. An increase in the level of WBV was seen in pre-DM and a progressive increase in the level of WBV was associated with different stages of DM. Oxidative stress was considered a factor accounting for the elevated WBV in diabetic subjects. The lack of difference in WBV between the diabetic group with and without CVD could be due to the fact that oxidative stress risk in DM is as high as that of diabetics with CVD. The effect of reactive oxygen species on erythrocyte deformability was demonstrated by the work of Srour et al. [78]. In their study, normal erythrocytes were incubated with 10 mM of hydrogen peroxide for 60 min at 37°C. Erythrocyte deformability was reduced after incubation and was correlated with lipid peroxidation [78]. Lipid peroxidation (and its secondary products such as malondialdehyde) can cause polymerization of membrane components and thus increase the aminophospholipid bilayer rigidity. This peroxidant injury initiated in the lipid component of the membrane can also be transmitted to neighboring substances such as membrane proteins [79,80]. These polymerization reactions are supposed to decrease cell deformability and consequently increase membrane rigidity. Spectrin, a major protein component of the erythrocyte membrane skeletal system, performs a variety of membrane functions, including the regulation of membrane deformability and stability [81]. Snyder et al. showed that change in deformability is related to membrane protein peroxidation [82]. Membrane proteins of diabetic erythrocytes, such as spectrin, ankyrin and protein 4.2, are heavily glycosylated compared with nondiabetic erythrocytes. Oxidative modification of spectrin due to its glycosylation was proposed as a reason for decreased erythrocyte deformability [83]. Hence, oxidative stress present in MetS could be responsible for abnormal erythrocyte morphology and reduced deformability. Reduction in deformability characteristics consequently increases WBV [20].

Chen and coworkers used a high-pressure oxygen-sealed chamber as an optimal environment for the generation of free radicals [84]. They incubated 2 ml of blood from ten healthy male
Discussion: the relationship between WBV & MetS

Obesity, DM and hypertension are the state of chronic inflammation [87–90] and oxidative stress [91–94]. Oxidative stress and elevated levels of proinflammatory cytokines produced in DM, hypertension and obesity induce endothelial dysfunction [95,96]. Bioavailability of nitric oxide is reduced in endothelial dysfunction [97]. Nitric oxide plays a role in improving erythrocyte deformability. This chain of events altogether reduces erythrocyte deformability [98]. The present authors propose that morphological changes of erythrocytes (conversion of discocytes to stomatocytes or echinocytes) could be a consequence of decreased erythrocyte deformability, oxidative stress and systemic inflammation. Morphologically abnormal erythrocytes could interact with the endothelium, further amplifying endothelial dysfunction and exaggerating the inflammatory cascade. These consequences altogether lead to increased WBV (Figure 1). Peripheral vascular resistance is increased when WBV increases, which ultimately increases the pumping requirement of the heart [27]. This results in high frictional force (shear stress) acting on the endothelium, further increasing the risk of CVD [99]. Nitric oxide production is increased by the endothelium in response to high shear stress [100]. An increase in nitric oxide has been reported in experimental animals with increased WBV [101,102]. Increased WBV is expected to have some positive effects on the vascular system and blood flow due to increased production of nitric oxide. This could be true in the case where there is an isolated increase in WBV. If increased WBV is the result of other underlying pathologies such as insulin resistance or dyslipidemia, which can cause endothelial dysfunction per se, then there is probably less chance of increased nitric oxide production due to a high shear stress response. For instance, the biochemical pathway that is responsible for insulin resistance is also responsible for diminished production of nitric oxide from the endothelium [103]. Hyperglycemia has also been reported to be a cause of diminished nitric oxide production in healthy human subjects without diabetes and insulin resistance [104]. In a study by Vekasi et al., WBV measured by a capillary viscometer was compared between patients with diabetic retinopathy taking aspirin and those not taking aspirin [105]. WBV, plasma viscosity, fibrinogen and Hct were significantly higher in the former compared with the latter patients. Aspirin improves endothelial dysfunction and improves progression of atherosclerosis and inflammation [106,107]. Reduction of WBV among patients taking aspirin may be due to the effects of aspirin aforementioned.

Bogar interestingly suggested that altered hemorheology and arterial hypertension do not have an exact cause–effect relationship but “are the two chickens from the same egg”; the egg being an overweight individual leading a sedentary lifestyle [108]. The author focused on the effect of obesity on hypertension and blood rheology. In other words, central obesity and lack of physical exercise are the main factors for insulin resistance [70]. The combined effect of
insulin resistance and obesity leads to MetS and altered hemorheology [109]. Hct-adjusted WBV was reported to be higher in subjects with MetS compared with those without MetS and increased with the increasing number of components of MetS [110]. Similarly, when subjects with MetS were categorized into different groups based on the number of positive components, it was found that the mean level of WBV was progressively increased in groups with a high number of positive components. WBV measurement was divided into four quartiles by percentage. The highest quartile of WBV occurred 4.8-times more frequently than the lowest quartile measurement among subjects with four MetS components. The highest quartile WBV measurement was positively associated with WC and negatively associated with HDLc. No significant association of highest quartile WBV measurement was found with blood pressure or plasma glucose level. The authors suggested that WBV at a high shear rate (200 s⁻¹) reflects mainly obesity and HDLc in subjects with MetS [111]. Elevated LDLc along with lipids associated with erythrocyte membrane deformity are prone to oxidization, thus stiffening the erythrocyte membrane. By contrast, HDLc has antioxidative [112] and anti-inflammatory properties [113]. HDLc plays a role in protecting integrity of the normal endothelium [114], maintaining the erythrocyte deformability characteristics [115] and, thus, has an inverse relationship with WBV. Another study showed that whole-blood filterability was significantly reduced whereas WBV, plasma and serum viscosity were significantly higher in the MetS group compared with controls. WBV was also found to be significantly correlated with homocysteine levels [116], one of the markers of endothelial dysfunction [117]. A complete hemorheological profile was studied in MetS subjects by Vaya et al. and they reported high corrected WBV, increased erythrocyte aggregation and reduced erythrocyte deformability in subjects with MetS compared with controls without MetS, who may have one or two components of MetS [118]. Inflammatory markers, such as C-reactive protein, fibrinogen, neutrophils and total leukocytes were significantly higher in MetS subjects compared with controls. Among five components of MetS, WC significantly predicted corrected WBV in MetS. A high level of inflammatory markers in MetS subjects and a strong association of WC with WBV emphasizes the role of central obesity and adipokines in hemorheological alterations.

Conclusion

There is indication that oxidative stress causes decreased erythrocyte deformability, which in turn results in sequentially altered erythrocyte morphology, increased WBV and, hence, further complicates the various components of MetS. There is a gap in the knowledge between the precise measures of erythrocyte deformability and its impact on WBV levels in the components of MetS. Specific studies in this direction would make a significant contribution to proposing an updated definition of MetS, keeping in mind the fact that MetS has a hemodynamic basis.

Future perspective

During the next 5 years, in addition to established biomarkers, WBV will be used to predict CVDs and complications. WBV could be a useful bioindicator in the assessment of MetS, its severity and progression. Increased CVD is the major outcome of MetS. Increase in WBV might be the prior event that leads to CVD in MetS and, thus, altered hemorheology can act as a bridge between cause (MetS) and
consequences (CVD). Altered hemorheology will certainly be incorporated in the definition of MetS in the coming years.

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Executive summary

**Diabetes mellitus & whole-blood viscosity**

- Glucose oxidation and protein glycation, caused by diabetes-associated hyperglycemia, may induce modifications in the mechanical and rheological properties of erythrocytes.

**Dyslipidemia & whole-blood viscosity**

- Although abnormal lipid profile has adverse effects on whole-blood viscosity (WBV), the association is not direct and depends on the complex interaction of dyslipidemia with other biochemical and metabolic factors.

**Obesity & WBV**

- Various components of metabolic syndrome and mostly central obesity contribute to decreased erythrocyte deformability.
- Adipokines, such as IL-6, TNF-α, plasminogen activator inhibitor-1 and proteins of the renin–angiotensin system secreted from adipose tissue, may alter the hemorheology through complex metabolic, endocrine and genetic interactions.

**Oxidative stress & WBV**

- Morphological changes of erythrocytes could be a consequence of decreased erythrocyte deformability, oxidative stress and systemic inflammation. Morphologically abnormal erythrocytes could interact with the endothelium, further amplifying endothelial dysfunction and exaggerating the inflammatory cascade. These consequences altogether lead to increased WBV.

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Papers of special note have been highlighted as:

* of interest
** of considerable interest

6. Large community-based study that associates whole-blood viscosity with insulin resistance syndrome.


Stamos TD, Rosenson RS. Low high density lipoprotein levels are associated with an elevated blood viscosity, Atherosclerosis 146(1), 161–165 (1999).


Hypertension


Whole-blood viscosity & metabolic syndrome


* This conference paper strongly puts forward the notion that the highest quartile of whole-blood viscosity is frequently associated with patients with four positive metabolic syndrome components.


