

Relationship

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11 Relationship between diabetes mellitus and blood viscosity as measured by the digital microcapillary® system

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Abstract. Chronic hyperglycemia in diabetes mellitus (DM) increases the risk of cardiovascular complications, including stroke. Blood viscosity is elevated in stroke; therefore, there may also be a relationship between DM and blood viscosity that influences stroke risk. This cross-sectional study compared blood viscosity and non-fasting blood glucose among three groups, diabetes patients and non-DM controls visiting the Integrated Community Health Post (Posbindu) East Pisangan primary healthcare clinic in January and March 2015 (collectively the Posbindu group) and healthy controls from a previous study on blood viscosity in stroke. Blood viscosity was examined by the Digital Microcapillary® system, a recently developed tool allowing for rapid and cost-effective measurement at local clinics. Blood viscosity was significantly higher in diabetes patients compared to the healthy controls ($p = 0.000$). However, there was no significant correlation between blood glucose and blood viscosity ($p = 0.221$) or a relationship between DM and blood viscosity among the Posbindu group ($p = 0.566$). This discrepancy may have been caused by other risk factors influencing blood viscosity in our non-DM controls. Further study is needed to identify these confounding factors. These results suggest that risk factors for high blood viscosity (aside from DM) are common in East Pisangan. In addition, the Digital Microcapillary® system proved effective for blood viscosity screening at a local healthcare clinic.

9 I. Introduction

Diabetes mellitus (DM) is a syndrome characterized by metabolic dysfunction and hyperglycemia due to insufficient insulin production or reduced insulin sensitivity. In 2013, the estimated number of DM patients reached 382 million worldwide. In Indonesia, there were 8.5 million DM patients in 2013, and this number is expected to increase to 14.1 million by 2035 [1]. Chronic hyperglycemia can cause numerous complications, of which cardiovascular disease is the most common DM-related cause of death and disability. Stroke is a major complication of DM, and the risk of stroke is 150%–400% higher in DM patients than in the age-matched non-DM population [2,3,4].

Viscosity is the resistance to flow resulting from internal friction. In DM patients, blood viscosity is elevated due to the decreased deformability and greater aggregation tendency of red blood cells [5]. Diabetes mellitus also causes microangiopathy and macroangiopathy, resulting in the narrowing of blood vessels. The combination of capillary narrowing and high blood viscosity leads to slower blood and erythrocyte flow. Slower erythrocyte flow in turn leads to the formation of rouleaux, which will increase hematocrit. Ultimately, blood and oxy-hemoglobin delivery to the brain is reduced, resulting in cerebral ischemia [6,7]. Therefore, increased blood viscosity may be an important pathogenic factor increasing stroke risk in DM patients.

There are several blood viscosity measurement instruments; however, these are available in large laboratories only and the results cannot be obtained immediately. In contrast, the Digital Microcapillary® (MD) is a more recently developed instrument that is easier to use, portable, and yields immediate results. A previous study using Digital Microcapillary® concluded that enhanced blood viscosity



accelerates clinical deterioration in acute ischemic stroke [8]. Thus, blood viscosity screening should be performed at all healthcare centers. This study examined blood viscosity among DM and non-DM populations to assess the potential relevance of high blood viscosity to stroke risk in DM. If there is a relationship, it is possible that the risk of stroke or the severity of stroke can be reduced by DM management that includes treatment of blood viscosity. In addition, this study evaluates the feasibility of Digital Microcapillary® for use by local primary health care facilities.

2. Methods

This is a cross-sectional study of three groups, DM patients, non-DM controls, and healthy controls. The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital. Measurement from DM patients and non-DM controls (n = 221 in total) were obtained by the Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, at Posbindu East Pisangan, Jakarta, in January and March 2015. The data consisted of non-fasting blood glucose and blood viscosity as measured by a glucose meter (Accutrend® Plus) and Digital Microcapillary®, respectively. The healthy controls were 40 adults with normal blood glucose and viscosity values obtained during physical and laboratory examinations at the Clinical Pathology Department, Faculty of Medicine, Universitas Indonesia [8]. The inclusion criteria for this study were patients visiting Posbindu East Pisangan (or healthy subjects investigated by Rasyid in 2014), age ≥ 17 years, and with available blood glucose and blood viscosity values as well as other required data [8]. Patients taking anticoagulants were excluded.

The independent variable for analysis was blood glucose and the dependent variable was blood viscosity. The confounding variables included were other risk factors that may increase blood viscosity such as hypertension, obesity, smoking, hypercholesterolemia, hyperuricemia. IBM SPSS Statistics version 21 was used to process and analyze the collected data. Spearman's correlation analysis was used to assess the relationship between blood glucose and viscosity. Blood glucose and viscosity values were also grouped into the categories DM/non-DM and hyperviscosity/non-hyperviscosity. Diabetes was defined by venous blood glucose ≥ 200 mg/dL or DM history [9]. The blood viscosity classification was based on reference values of 4.85–5.09 poise for males and 4.37–4.70 poise for females, with values above the upper limit defined as hyperviscosity [8].

3. Results

Characteristics of the Posbindu East Pisangan subjects. In total, 221 patients visited Posbindu East Pisangan in January and March 2015, of which 21 visited twice. One patient was excluded for incomplete data and four for taking anticoagulants. Thus, this study involved 195 patients from the local clinic. Table 1 presents the age distribution, sex, and DM status of these participants.

Table 1. Posbindu demographics and diabetes mellitus status.

Characteristic	Subject Frequency (%)	Median (Min–Max)
Sex		
Male	40 (20.5%)	
Female	155 (79.5%)	
Age (years)		50 (18–79)
Diabetes mellitus		
Yes	36 (18.5%)	
No	159 (81.5%)	
Men	8 (22.2%)	
Women	28 (77.8%)	
<25 years old	0 (0%)	
25–44 years old	2 (5.55%)	
45–59 years old	24 (66.67%)	
≥60 years old	10 (27.78%)	
Old cases of diabetes mellitus		
Blood glucose <200 mg/dL	23 (63.9%)	
Blood glucose ≥200 mg/dL	10 (27.8%)	
New cases of diabetes mellitus	3 (8.3%)	

Most of the subjects were female (79.5%), median age was 50 years, and 36 (18.5%) were diabetic, with peak prevalence in the 45–59 year age range. Most of the DM cases were diagnosed based on anamnesis history (33, 91.7%) while three new cases were identified by non-fasting blood glucose ≥ 200 mg/dL. Most of the DM patients were old cases with blood glucose <200 mg/dL.

Table 2. Distribution of non-fasting blood glucose and viscosity values for the Posbindu subjects.

Characteristic	Mean (SD) or Median (Min–Max)
Non-fasting blood glucose level (mg/dL)	
All subjects	82 (49–369)
Diabetes mellitus	160 (49–369)
Non-diabetes mellitus	79 (52–199)
Blood viscosity value (poise)	
All subjects	6.17 (3.04–8.67)
Diabetes mellitus	6.14 (1.19)
Non-diabetes mellitus	6.17 (3.04–7.92)

Normality of data distributions was assessed by X

Table 2 shows the distributions of non-fasting blood glucose and blood viscosity values for the Posbindu group. Median non-fasting blood glucose was substantially higher (160 mg/dL) in the DM patients than in the non-DM subjects (160 vs. 79 mg/dL). The mean blood viscosity value in the DM patients was 6.14 poise. The blood viscosity values in both of the groups were above the normal range.

Table 3. Distribution of blood viscosity values for the Posbindu subjects.

Characteristic	Subject Frequency	Mean (SD) or Median (Min–Max) Blood Viscosity Value (poise)
All Subjects		
Blood hyperviscosity	173 (88.7%)	
Non-blood hyperviscosity	22 (11.3%)	
Diabetes mellitus		
Blood hyperviscosity	31 (86.1%)	6.41 (1.03)
Non-blood hyperviscosity	5 (13.9%)	4.44 (0.45)
Non-diabetes mellitus		
Blood hyperviscosity	142 (89.3%)	6.30 (4.73–7.92)
Non-blood hyperviscosity	17 (10.7%)	4.51 (3.04–4.89)

Normality of data distributions assessed by X

Most of the subjects had blood viscosity values above the reference values (88.7%) and the majority of the DM and non-DM subjects were classified with blood hyperviscosity (86.1% and 89.3%, respectively) (Table 3). The healthy controls from the study of Rasyid (2014) had blood glucose and viscosity values within normal limits (Table 4) and the proportion with blood hyperviscosity was significantly lower than in the DM group ($p = 0.000$ by Chi-square test).

Table 4. Blood viscosity status of Posbindu DM patients and healthy controls.

		Blood Viscosity		p ^a
		Blood Hyperviscosity	Non-blood Hyperviscosity	
		n	n	
Blood Glucose	Diabetes Mellitus	31	5	0.000
	Healthy Controls	0	40	
	Total	31	45	

^aChi-square test

The correlation between blood glucose and blood viscosity among Posbindu East Pisangan subjects was not significant ($p = 0.221$ by Spearman's test) (Figure 1).

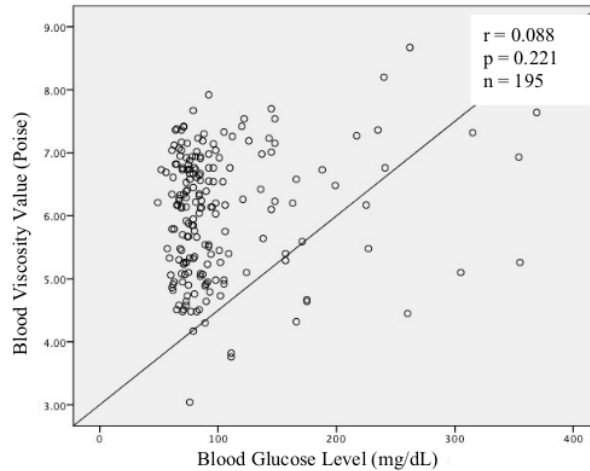


Figure 1. Correlation between blood glucose and viscosity from Posbindu data.

Furthermore, there was no significant relationship between DM status and blood viscosity in this group ($p = 0.566$) (Table 5).

Table 5. Diabetes status versus blood viscosity in Posbindu subjects.

		Blood Viscosity		p^a
		Blood Hyperviscosity	Non-blood Hyperviscosity	
Blood Glucose	Diabetes Mellitus	n 31	n 5	0.566
	Non-diabetes Mellitus	142	17	
	Total	173	22	

^aFisher's test

4. Discussion

Digital Microcapillary[®] is a self-contained portable instrument that allows for rapid and cost-effective measurement of blood viscosity at any local healthcare facility. Rasyid (2014) demonstrated the accuracy and reliability of Digital Microcapillary[®] for measuring blood viscosity [8]. Thus, Digital Microcapillary[®] will enable more extensive study of blood viscosity changes in disease.

There are several DM prevalence estimates in Indonesia, including clinical diagnosis rate based on a population survey (1.5%), surveys of doctor's diagnosis or typical symptoms such as of polyuria, polydipsia, polyphagia, and (or) weight loss (2.1%), and estimates based on blood glucose examination (6.9%) [10]. Given the higher rate of hyperglycemia, the prevalence of DM may be far greater than the clinical diagnosis rate. In this study, the DM was determined by non-fasting blood glucose ≥ 200 mg/dL or previous diagnosis. Using this definition, 18.5% of the study population visiting Posbindu East Pisangan in January and March 2015 were diabetic, again suggesting a prevalence far higher than the clinical diagnosis rate in this region of Indonesia.

There was a significant difference in blood viscosity between our DM cohort and the healthy controls studied by Rasyid (2014), a group receiving physical and laboratory examinations to verify that viscosity

and blood glucose values were within normal limits. These results are consistent with a study conducted by Kostova et al. (2012) who found higher mean blood viscosity in the DM patients compared to healthy subjects across the shear rates range. This elevated viscosity in the DM is due to an increase in hematocrit, fibrinogen, and erythrocyte count, greater erythrocyte aggregation propensity, and decreased erythrocyte deformability [11]. Le Devehat et al. (2004) also found that DM patients exhibit multiple hemorheological disturbance even before microangiopathy or macroangiopathy, including increased erythrocyte aggregation and fibrinogen levels [12].

However, we found no significant difference in blood viscosity between the DM patients and a non-DM cohort visiting a primary healthcare center. Furthermore, there was no significant correlation between blood glucose and blood viscosity among this group. The participants visiting Posbindu were considered non-DM if blood glucose was <200 mg/dL and had never been diagnosed previously with DM. Thus, these non-DM controls may have multiple risk factors affecting blood viscosity, obscuring any correlation between blood glucose and viscosity. Such risk factors include hypercholesterolemia, hyperuricemia, hypertension, obesity, and smoking, which were the confounding factors in this study. Indeed, previous studies support effects of these factors on blood viscosity. Moreover, hypertension, dyslipidemia, obesity, and DM are major components of metabolic syndrome, and all can damage the microcirculation [9].

Thus, the lack of a significant relationship between blood glucose and viscosity suggests that the non-DM subjects have additional risk factors for high blood viscosity. Indeed, the vast majority of the non-DM controls exhibited blood hyperviscosity (89.3%), suggesting that these risk factors are common in East Pisangan, Jakarta. Given the high blood viscosity in stroke patients found by Rasyid (2014), we suggest that stroke risk factors are unacceptably high in East Pisangan [8]. This study also verifies the feasibility of using Digital Microcapillary® at primary healthcare facilities for screening blood viscosity as a possible risk factor for DM and associated cerebrovascular complications.

Conclusion

Blood viscosity was significantly elevated in the DM patients compared to the healthy controls when the health status of the controls was verified by comprehensive physical and laboratory examinations. However, no such relationship was found in a sample visiting a primary healthcare facility, suggesting that other risk factors for high blood viscosity are common in the study area. The Digital Microcapillary® system is a valuable instrument for blood viscosity screening due to its portability, convenience, and rapid measurement capacity.

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