Blood Viscosity, Glycemic Markers and Blood Pressure: A Study in Middle-Aged Normotensive and Hypertensive Type 2 Diabetics

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Abstract Altered blood viscosity (BV) may affect blood pressure (BP) and develops further complications in diabetes. A case-control study was performed to examine the relationship of erythrocyte sedimentation rate (ESR), hematocrit, fibrinogen, and BV with glycemic markers and BP in middle-aged normotensive and hypertensive type 2 diabetic patients and healthy controls. A total of 145 participants between age group 30–50 years divided into three groups; controls (n = 60), type 2 diabetes mellitus (T2DM, n = 55), and T2DM with hypertension (T2DM + HTN, n = 30). ESR and hematocrit were determined by Wintrobe's method. Plasma fibrinogen was measured using Lempert method and BV calculated using Merrill's formula. T2DM and T2DM + HTN patients had higher fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), ESR, and fibrinogen compared to controls. In both male and female SBP, DBP, MAP, FPG, and HbA1c were significantly higher in T2DM and T2DM + HTN groups, compared to controls. Further, linear regression analysis revealed a positive association of ESR and fibrinogen with SBP, DBP, MAP, FPG, HbA1c, and positive diabetic status in all participants. Also, in the same analysis, BV showed a positive association with SBP, DBP,

and MAP. The association of ESR and fibrinogen with glycemic markers and BP in diabetes supporting the value of emerging marker's for early prediction of T2DM and hypertension.

Keywords Blood pressure · Blood viscosity · Middle-aged · Fibrinogen · Glycemic markers · Hypertension · Type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a complex endocrine disorder characterized by hyperglycemia as well as insulin resistance [1]. Uncontrolled T2DM is the major cause of various complications such as dyslipidemia, obesity, hypertension, and cardiovascular diseases (CVD) [2]. Among all, hypertension is most common in diabetes, caused by an increase in peripheral vascular resistance, determined by arterial vessel tone and blood viscosity (BV) [3]. BV is the intrinsic resistance to blood flow developed due to the frictional force between adjacent layers of flowing blood. As blood is a non-Newtonian fluid, its viscosity depends on the shear rate. Abnormally high BV can damage the vessel wall because the heart is overloaded to pump blood in the vascular bed [4].

Growing number of evidence have suggested that BV is increased in pre-diabetes [5, 6] and diabetes [7–9]. Recently, a large prospective study has suggested that BV and hematocrit are risk factors for T2DM. They determined that participants in the highest quartile of BV were 60% more likely to develop diabetes than their counterparts in the lowest quartile [10]. Similar findings were obtained in smaller or selected populations [11, 12]. These

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observations suggested that the elevation in BV might be a risk factor for diabetes.

Variations in BV can change shear stress on the endothelium, which subsequently alters production of vasoactive materials such as nitric oxide (NO), prostacyclin, and endothelin, directly affecting microvascular diameter. Therefore, variations in BV may play a key role in peripheral vascular resistance [3]. Thus, the present study was aimed to evaluate the association of BV with glycemic markers and BP in middle-aged normotensive and hypertensive T2DM patients in Maharashtra, Western part of India.

Materials and Methods

Study Design and Population

The present case-control study was conducted at Symbiosis School of Biological Sciences, Symbiosis International (Deemed University), Pune, India. We recruited 145 participants, including male and female aged 30–50 years, from private diabetic clinics and local regions of Pune, India. Participants were allocated into three different groups as healthy controls ($n = 60$), T2DM patients ($n = 55$), and T2DM patients with hypertension (T2DM + HTN, $n = 30$). Participants had no prior history of T2DM, hypertension, and any other chronic medical condition were considered as healthy controls. T2DM group included patients with HbA1c levels $\geq 6.5\%$ or had a current fasting blood glucose (FPG) level ≥ 7 mmol/L, but no other complications. T2DM + HTN group included patients with a proven history of T2DM with hypertension. Hypertension defined as those with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and those receiving antihypertensive medications.

The study was performed in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Independent Ethics Committee (Institutional Ethics Committee), of Symbiosis International (Deemed University), Pune, India. Informed consent obtained from all participants included in the study. Data including age, sex, duration and family history of diabetes and hypertension, lifestyle-related information, physical exercise, and addiction were also collected. Addictive habits assessed by asking questions on alcohol consumption, smoking, and tobacco chewing. Smokers in India consume tobacco in various forms. Therefore, users of all types of tobacco products and present and past smokers were included in smoker category.

Anthropometric Measurements

Body weight, height, waist, and hip circumferences were measured. The body mass index (BMI) was computed as weight (in kg) divided by square of the height in meters [$\text{weight}/(\text{height})^2$]. Waist circumference (WC) was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest using a non-stretchable measuring tape. Hip circumference (HC) was measured at the level of greater trochanters. Waist to hip ratio (WHR) was calculated as WC (cm) divided by HC (cm) and waist-to-height ratio (WHtR) calculated as WC (cm) divided by height (cm).

Blood Pressure Measurement

SBP and DBP were measured twice with a validated automatic digital blood pressure monitor (Omron Hem8712) and the average of two readings was used for analysis. Mean arterial blood pressure (MAP) was determined using the relationship, $\text{MAP} = P_{\text{diastolic}} + 1/3(P_{\text{systolic}} - P_{\text{diastolic}})$ [13].

Analysis of Biochemical Variables

Blood samples were obtained after overnight fasting (10–12 h) with minimum stasis to avoid the influence of postprandial lipid increase on hemorheological parameters. Glycated hemoglobin (HbA1c) measured by the enzymatic immunoturbidometric method (Randox reagent kit). Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG) were measured by enzymatic kit methods (Span diagnostics reagent kits). Direct low-density lipoprotein cholesterol (LDL-c) measured by the enzymatic method (Span diagnostics reagent kits). Plasma fibrinogen level was estimated by the Lempert method [14]. Erythrocyte sedimentation rate (ESR) and hematocrit were determined by Wintrobe's method. The BV was calculated by Merrill's formula [8]: $\text{BV (YSS)} = [13.5 \times 10^{-6} \times (\text{fibrinogen concentration, gm \%})^2 \times (\text{hematocrit}-6)^3]$, where YSS = Yield shear stress.

Statistical Analysis

SPSS version 16.0 software was used for statistical analysis. Variables were summarized as the mean and standard deviation (mean $\pm$ SD) and one-way analysis of variance (ANOVA) test was used to determine significant differences between the means of three independent groups. Proportions were compared using Chi square test. Spearman's rank correlation coefficients were calculated. Linear regression analysis used to examine the association of ESR,

hematocrit, fibrinogen, and BV with BP and glycemic markers in all participants. A two-sided test of significance was used and p value < 0.05 considered as significant.

Results

Baseline and Biochemical Characteristics of the Study Population

Baseline and biochemical characteristics of controls, T2DM, and T2DM + HTN groups were presented in Tables 1 and 2. There were significant differences in BMI, WC, HC, WHtR, TG, and VLDL-c, while no significant differences were observed in WHR, TC, HDL-c, and LDL-c. Highest percentage of smoking (16%) and alcohol consumption (25%) were observed in T2DM and control groups, respectively (Table 1). One-way ANOVA with post hoc Bonferroni test was performed to compare control, T2DM, and T2DM + HTN groups. Both T2DM and T2DM + HTN groups had significantly higher SBP, DBP, MAP, FPG, HbA1c, ESR, and fibrinogen compared to controls. There were no significant differences in hematocrit and BV (Table 2).

Sex-Wise Distribution of Biochemical Variables

Blood pressure and other biochemical variables were compared in controls, T2DM, and T2DM + HTN groups for each sex using ANOVA test. In both male and female SBP, DBP, MAP, FPG, and HbA1c were significantly higher in T2DM and T2DM + HTN, compared to controls. ESR, fibrinogen, and hematocrit were significantly different among female while only hematocrit was significantly different in the male. In both male and female, there was no significant difference in BV (Table 3).

Correlation Analysis

Spearman's rank order correlation analysis was used to determine the correlation of ESR, fibrinogen, hematocrit, and BV with BP and glycemic markers (FPG and HbA1c) in all participants. There was a significant positive correlation of ESR and fibrinogen with SBP, DBP, MAP, FPG, and HbA1c in all participants. Hematocrit showed a significant negative correlation with age, sex, FPG, and HbA1c (Table 4).

Table 1 Baseline characteristics of study population

Variables	Controls	T2DM	T2DM + HTN	p value
Number	60	55	30	–
Age (years)	39 $\pm$ 6	41 $\pm$ 6	43 $\pm$ 6	0.007
Male/female (%)	52/48	60/40	50/50	0.702
BMI (Kg/m ²)	25.6 $\pm$ 3.9	27.2 $\pm$ 3.3	28.6 $\pm$ 4.8	0.002
WC (cm)	90.12 $\pm$ 9.5	91.29 $\pm$ 14.3	98.15 $\pm$ 8.5	< 0.001
HC (cm)	97.7 $\pm$ 10.4	99.7 $\pm$ 7.7	105 $\pm$ 6.4	0.001
WHR	0.93 $\pm$ 0.06	0.92 $\pm$ 0.14	0.93 $\pm$ 0.06	0.948
WHtR	0.56 $\pm$ 0.06	0.57 $\pm$ 0.09	0.62 $\pm$ 0.05	< 0.001
Smoking (Y/N, %):	3/97	16/84	3/97	0.022
Alcohol consumption (Y/N, %):	25/75	15/85	7/93	0.076
FH of T2DM (Y/N, %):	37/63	80/20	87/13	< 0.001
FH of HTN (Y/N, %):	18/82	18/82	50/50	0.002
TG (mmol/L)	1.24 $\pm$ 0.43	1.6 $\pm$ 0.88	1.55 $\pm$ 0.63	0.032
TC (mmol/L)	3.83 $\pm$ 0.93	3.9 $\pm$ 0.9	4 $\pm$ 0.98	0.679
HDL-c (mmol/L)	1.05 $\pm$ 0.2	0.99 $\pm$ 0.2	1.02 $\pm$ 0.32	0.184
LDL-c (mmol/L)	2.4 $\pm$ 0.9	2.2 $\pm$ 0.89	2.28 $\pm$ 0.89	0.487
VLDL-c (mmol/L)	0.57 $\pm$ 0.2	0.73 $\pm$ 0.4	0.71 $\pm$ 0.29	0.032

Continuous variables were summarized as mean $\pm$ SD. Categorical variables were presented in percentage (%). One-way analysis of variance (ANOVA) test was used to determine significant differences between the means of three independent groups. Proportions were compared using Chi square test. p -value < 0.05 considered as significant. Significant p values were shown in bold

BMI body mass index, WC waist circumference, HC hip circumference, WHR waist to hip ratio, WHtR waist to height ratio, FH family history, Y/N yes/no

Table 2 Group-wise comparison of blood pressure and biochemical variables

Variables	Control	T2DM	T2DM + HTN	<i>p</i> value (Controls vs T2DM)	<i>p</i> value (Controls vs T2DM + HTN)	<i>p</i> value (T2DM vs T2DM + HTN)
SBP (mmHg)	120.7 ± 7.2	126 ± 5.7	137 ± 17	0.004	< 0.001	< 0.001
DBP (mmHg)	78 ± 5.7	83.4 ± 4.6	86 ± 7	< 0.001	< 0.001	0.09
MAP (mmHg)	92.4 ± 5.3	97.7 ± 3.9	103.4 ± 9.3	< 0.001	< 0.001	< 0.001
FPG (mmol/L)	4.7 ± 0.57	8.3 ± 2.7	7.2 ± 1.76	< 0.001	< 0.001	0.049
HbA1c (%)	5.1 ± 0.43	7.98 ± 1.2	8 ± 1.16	< 0.001	< 0.001	1.00
ESR (mm/hr)	11.2 ± 9.4	21.5 ± 10.7	20.9 ± 12.9	< 0.001	< 0.001	1.00
Hematocrit (%)	43.1 ± 5.1	43.1 ± 6.5	42.5 ± 6.5	1.00	1.00	1.00
Fibrinogen (g/L)	2.7 ± 0.6	3.1 ± 0.7	3.5 ± 0.9	0.027	< 0.001	0.057
BV (YSS/dyne-cm ²)	0.059 ± 0.036	0.067 ± 0.07	0.085 ± 0.08	1.00	0.201	0.574

Continuous variables were summarized as mean ± SD. One-way ANOVA with post hoc Bonferroni test was performed to compare control, T2DM, and T2DM + HTN groups. *p*-value < 0.05 considered as significant. Significant *p* values were shown in bold

SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, FPG fasting plasma glucose, HbA1c glycated hemoglobin, ESR erythrocyte sedimentation rate, BV blood viscosity

Table 3 Sex-wise distribution of blood pressure, blood viscosity, and other biochemical variables in three different groups

Variables	Controls	T2DM	T2DM + HTN	<i>p</i> value
Male				
Number	31	33	15	–
ESR (mm/hr)	12.7 ± 10.7	18 ± 8.5	16 ± 12.4	0.117
Fibrinogen (mg/dL)	2.9 ± 0.56	3.1 ± 0.7	3.2 ± 0.87	0.278
Hematocrit (%)	43.6 ± 4.9	42 ± 5.5	45.8 ± 6.2	0.091
BV (YSS/dyne-cm ²)	0.064 ± 0.027	0.076 ± 0.088	0.11 ± 0.11	0.139
FPG (mmol/L)	4.67 ± 0.59	8.7 ± 2.58	7.55 ± 2	< 0.001
HbA1c (%)	5.05 ± 0.5	8.13 ± 1.14	7.99 ± 1.14	< 0.001
SBP (mmHg)	122 ± 6	128 ± 6	138 ± 14.8	< 0.001
DBP (mmHg)	79 ± 5.1	88 ± 5	88.5 ± 6.6	< 0.001
MAP (mmHg)	94 ± 4.5	98 ± 4.3	105 ± 8.6	< 0.001
Female				
Number	29	22	15	–
ESR (mm/hr)	9.5 ± 7.5	27 ± 11.5	26 ± 11.8	< 0.001
Fibrinogen (mg/dL)	2.6 ± 0.5	3.2 ± 0.9	3.7 ± 0.9	< 0.001
Hematocrit (%)	42.6 ± 5.3	39 ± 6.3	37 ± 3.2	0.004
BV (YSS/dyne-cm ²)	0.055 ± 0.043	0.053 ± 0.032	0.059 ± 0.03	0.882
FPG (mmol/L)	4.66 ± 0.55	7.79 ± 2.8	6.93 ± 1.48	< 0.001
HbA1c (%)	5.2 ± 0.5	7.78 ± 1.28	8.01 ± 1.22	< 0.001
SBP (mmHg)	119 ± 7.9	125 ± 5.5	138 ± 16.6	< 0.001
DBP (mmHg)	78 ± 6.3	84 ± 4.1	83.9 ± 7.1	< 0.001
MAP (mmHg)	92 ± 5.3	97 ± 3.6	102 ± 10	< 0.001

Table 4 Correlation of ESR, fibrinogen, hematocrit, and BV with blood pressure and glycemic markers in all participants

Variables	ESR		Hematocrit		Fibrinogen		BV	
	ρ	<i>p</i> value	ρ	<i>p</i> value	ρ	<i>p</i> value	ρ	<i>p</i> value
Age	0.144	0.083	– 0.178	0.031	– 0.021	0.801	– 0.184	0.026
Sex	0.125	0.132	– 0.277	0.001	– 0.058	0.486	– 0.190	0.021
SBP	0.284	0.001	– 0.055	0.513	0.273	0.001	0.120	0.151
DBP	0.291	< 0.001	0.015	0.853	0.207	0.012	0.146	0.079
MAP	0.344	< 0.001	– 0.021	0.799	0.229	0.005	0.126	0.130
FPG	0.321	< 0.001	– 0.184	0.026	0.248	0.003	0.029	0.729
HbA1c	0.356	< 0.001	– 0.209	0.011	0.305	< 0.001	0.050	0.550

ρ = Spearman's correlation coefficient. *p*-value < 0.05 considered as significant. Significant *p* values were shown in bold

Linear Regression Analysis

Linear regression analysis was performed to test the causal relationship of ESR, hematocrit, fibrinogen, and BV with BP, glycemic markers, and diabetic status (absence of diabetes was coded as 0 and presence of diabetes was coded as 1) in all participants. A linear association of ESR and fibrinogen with BMI, SBP, DBP, MAP, FPG, HbA1c, and positive diabetic status was observed. In addition, BV showed a positive association with SBP, DBP, and MAP in all participants (Table 5).

Discussion

BV affects blood flow both at large arteries and in micro-circulation [8]. Many studies have investigated BV in pre-diabetic [5], diabetic [15, 16] and hypertensive individuals [17–19], and researchers have found an alteration of BV in T2DM. Hyperglycemia increases the osmolarity of the blood, which further increases the capillary permeability, hematocrit and subsequently the BV [8]. According to Poiseuille's law, the rate of blood flow is inversely related to BV. Therefore, decreased blood flow, in turn, decreases the delivery of insulin, glucose, and oxygen to skeletal muscle [20]. Compensatory mechanisms to increase blood flow would include vasodilatation and elevation in BP [21, 22]. Once these mechanisms are reached to their maximum, the concentration of glucose and insulin can increase and further returns to their normal delivery [23]. Therefore, an increase in BV is a sufficient cause of increased glucose and insulin when other compensatory mechanisms are not sufficient to maintain blood flow at optimal levels. However, oxygen delivery cannot increase, because an increased hemoglobin concentration would lead to increase in viscosity. Therefore, increased hematocrit levels and in turn, a further increase in viscosity might be a compensatory mechanism to a primary decrease in

oxidative capacity. In diabetes, persistent hyperglycemia exposes RBCs to elevated blood glucose, thus resulting in glycation of hemoglobin, fibrinogen, prothrombin, and other proteins involved in clot-ting mechanisms. Significant elevations of ESR and fibrinogen might be due to the variety of morphological changes exhibited by RBCs and compositional changes in plasma associated with T2DM [24].

In the present study groups a significant difference was observed in BMI, WC, HC, WHtR, TG, and VLDL-c. Among all study groups most of the participants were not having any addictive habit (alcohol consumption and smoking). Very less numbers of participants have these addictive habits. Alcohol consumption is responsible for disruption of glucose homeostasis and insulin resistance, which further affects altered appetite that regulates the peptides and neurotrophic factors. Some studies have reported harmful effects of alcohol consumption on pancreatic beta-cells and stated that alcohol inhibits the insulin secretion [25]. Furthermore, smoking is associated with glucose intolerance, impaired FPG, and T2DM, and may alter BV [5, 26].

Additionally, a significant increase was reported in SBP, DBP, MAP, FPG, HbA1c, ESR, and fibrinogen in T2DM and T2DM + HTN groups as compared to controls. While, no significant difference was observed for TC, HDL-c, LDL-c, hematocrit. Also, for BV no significant difference observed for the group-wise comparison of control, T2DM and T2DM + HTN groups. The insignificant differences observed due to the fact that T2DM patients with hypertension have well-controlled hypertension and they were on anti-hypertensive therapy (beta-blockers, calcium channel blockers (CCBs), angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors). Beta-blockers exerts its BP lowering effect through blocking beta-1 adrenergic receptors and results in slower heart rate, reduced cardiac contractility, and decreased cardiac output. CCBs prevents the entry of calcium into

Table 5 Linear regression analysis of ESR, hematocrit, fibrinogen, and BV with BP and glycemic markers in all participants

Variables	Age	Sex	BMI	SBP	DBP	MAP	FPG	HbA1c	Diabetic status
ESR									
B	0.241	3.520	0.680	0.291	0.581	0.538	1.074	2.281	10.217
SE	0.158	1.935	0.236	0.085	0.144	0.128	0.379	0.543	1.790
Beta	0.126	0.150	0.233	0.274	0.319	0.331	0.230	0.330	0.430
<i>p</i> value	0.130	0.071	0.005	0.001	< 0.001	< 0.001	0.005	< 0.001	< 0.001
<i>t</i> value	1.522	1.819	2.875	3.421	4.044	4.206	2.831	4.198	5.709
Hematocrit									
B	− 0.148	− 3.239	0.007	0.010	0.078	0.049	− 0.305	− 0.513	− 2.037
SE	0.078	0.929	0.120	0.044	0.075	0.067	0.191	0.281	0.965
Beta	− 0.157	− 0.279	0.005	0.018	0.087	0.061	− 0.132	− 0.150	− 0.173
<i>p</i> value	0.059	0.001	0.955	0.828	0.297	0.463	0.113	0.070	0.037
<i>t</i> value	− 1.905	− 3.487	0.056	0.218	1.048	0.736	− 1.596	− 1.824	− 2.111
Fibrinogen									
B	0.111	0.003	0.047	0.029	0.041	0.045	0.070	0.136	0.505
SE	0.129	0.129	0.015	0.005	0.009	0.008	0.025	0.036	0.123
Beta	0.071	0.002	0.243	0.416	0.342	0.417	0.227	0.299	0.323
<i>p</i> value	0.391	0.980	0.003	< 0.001	< 0.001	< 0.001	0.006	< 0.001	< 0.001
<i>t</i> value	0.806	0.025	3.011	5.489	4.374	5.507	2.794	3.765	4.096
Log (BV)									
B	− 0.006	− 0.123	0.011	0.007	0.012	0.011	0.005	0.013	0.042
SE	0.004	0.048	0.006	0.002	0.004	0.003	0.010	0.014	0.049
Beta	− 0.135	− 0.210	0.154	0.247	0.255	0.279	0.045	0.079	0.071
<i>p</i> value	0.105	0.011	0.063	0.003	0.002	0.001	0.586	0.346	0.391
<i>t</i> value	− 1.632	− 2.582	1.876	3.055	3.171	3.481	0.546	0.945	0.860

B unstandardized coefficients, *SE* standard error, *Beta* standardized coefficients, Significant *p* values were shown in bold

vascular smooth muscles, which results in vasodilation and reduced vascular contractility, while ARBs block binding of angiotensin II to its receptor, and prevent vasoconstriction and fluid retention. ACE inhibitors block conversion of the inactive angiotensin I to the active angiotensin II and exert its BP-lowering effects [27]. Also, diabetic patients from both T2DM and T2DM + HTN groups were on lipid-lowering drugs, which may lower TC, hematocrit, and BV. In our study, participants with increased BP has low hematocrit, which reflects the condition in which vasodilation is no longer able to counteract the increase in vascular resistance due to increased BV [3]. Many studies have determined the positive association of BP and glycemic markers either with BV, fibrinogen or hematocrit [3, 5, 19]. Very few studies have conducted in middle-aged population from Pune, Western part of India. Development of diabetes at a young age increases the risk of developing further complications at a relatively young age. This leads to severe morbidity and early mortality in the most productive years of life.

Previous evidences have shown that diabetes and hypertension are associated with relative hyper-viscosity, [15–17, 28, 29]. To further confirm the causal relationship of ESR, fibrinogen, hematocrit, and BV with BP, glycemic markers, and positive diabetic status linear regression analyses were performed. The linear regression analysis revealed a positive association of ESR and fibrinogen with SBP, DBP, MAP, FPG, HbA1c, and positive diabetic status. BV showed a positive association with blood pressure (SBP, DBP, and MAP). Martini et al. [29] showed that BP response could be directly linked to the production of NO by the endothelium and therefore presumably the changes in shear stress in the circulation. Further research is needed to explore the relationship with larger sample size in each group. The strength of the present study is to assess major determinant of BV such as ESR, fibrinogen, and hematocrit along with BV in three different groups (control, T2DM, and T2DM + HTN) and determine their causal relationship with BP and glycemic markers in middle-aged population from Pune, a metropolitan city of India. There were some limitations to our study. First, it is a single-center

one-point time study and does not determine the causality. Second, the small sample size in each group.

Conclusion

In the light of the increased global prevalence of diabetes and its effect on cardiovascular mortality/morbidity, early detection, and effective prevention is one of the major strategy in public healthcare management. Thus, the routine blood test for blood viscosity and other cardiovascular risk markers might be an effective prevention strategy in middle-aged peoples suffering from T2DM for the prevention of further complications.

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