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THE INFLUENCE OF GLICATED HEMOGLOBINE ON WHOLE BLOOD VISOSITY IN PATIENTS WITH DIABETIC NEPHROPATHY

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ABSTRACT

The complications, especially those affecting microcirculation, exhibit great importance in the assessment and follow-up of patients with diabetes mellitus. Blood viscosity plays its most important role in the microcirculation where it contributes significantly to peripheral resistance and may cause sludging in the post capillary venules. The effect of whole blood viscosity in patients whit diabetic nephropaty is still unclear.

The aim of this study was to examine the influence of glicaemic control measured by glicated hemoglobin on rheological parameters, and especially on whole blood and plasma viscosity in patients with diabetic nephropaty. Blood viscosity is an important determinant of local flow characteristics. Blood exhibits shear thinning behavior: its viscosity decreases exponentially with increasing shear rates.

Estimation of whole blood and plasma viscosity was made on 42 patients, comparing different stages of diabetic nephropathy and with different values of glicated hemoglobin.

Depression of the regulatory mechanisms of microvascular blood flow as well as decreased tissue perfusion indicated the restricted blood flow in microcirculatory network in diabetic nephropathy. In conclusion blood viscosity was elevated in the patients with major organ complications and not in the patients without or with early complications, in correlation with poor glicaemic control.

Keywords: glicated hemoglobin; blood viscosity; diabetic nephropathy

Introduction

Diabetes mellitus (DZ) is a metabolic disease with one of the highest prevalence in industrialized countries and is a public health problem affecting developed countries. The prevalence of diabetes by 2014 was affected by about 387 million individuals globally, accounting for about 11% of the total population, requiring spending of about $ 612 billion (1, 2). It is believed that by 2030, the prevalence of this disease will increase significantly to the impact of more than 552 million individuals, accounting for about 15% of the total population, including about 183 million people not yet in evidence with this affection (1,2,3,4) and requires the allocation of more than $ 627 billion globally. It should also be stressed that the death rate caused by approximately 1/5 of all deaths worldwide (3, 4, 5). In Romania, according to the study PREDATORR (Diabetes Prevalence, Prediabet, Overweight, Obesity, Dyslipidemia, Hyperuricaemia and Chronic Kidney Disease), in 2013, diabetes had a 2.7% prevalence in the age group of 20- 39, increasing with age, reaching 17.6% in the 60-79 age group. According to CNAS in Romania between 2006 and 2016, the number of people for whom diabetes treatments have been reimbursed has doubled and the necessary costs have increased 6 times.

Renal involvement in diabetes occurs in approximately 30% of patients and is an important cause of chronic renal failure. Affecting hemorheological parameters leads to a change in the hemodynamic profile from both macro and microcirculation(6).

Hemorholoagical disorders favor the reduction of blood flow especially in capillaries, this being implicated in the etiology of hypoperfusion at this level and endothelial dysfunction (7), resulting in the appearance of new capillaries.

Material and methods

Patients

The proposed study is a prospective study in which we included a total of 42 diabetic patients with chronic kidney disease at different stages of development, patients of the family medicine cabinet, patients admitted to the Constanta Emergency Clinical Hospital and also patients in the Diaverum Center of Dialysis Constanta.

Three groups of diabetic patients with varying degrees of renal impairment were tested and analyzed for biological and rheological tests:

- lot no. 1 including 10 diabetic patients without renal impairment or mild renal impairment classified as Chronic Renal Disease at Stage 0/1 with an GFR of > 90ml / min / 1.73m2 and with chronic renal disease in Stage 2 with an GFR of up to 90ml / min / 1.73m2
- lot no.2 including 18 diabetic patients with diabetic nephropathy and moderate renal impairment with GFR between 30-60 ml / min / 1.73m2
- lot no. 3 including 14 patients with severe or terminal renal insufficiency with GFR <30 ml / min / 1.73m2

Method

The viscometer used for rheological determinations is a Brookfield DV-II + Pro which performs measurements at different rotational speeds and, implicitly, shear rates (sheare rate: from 18.8 to 800sec-1)

Figure 1 Viscometer Brookfield DV-II+Pro http://www.brookfieldengineering.com/products/viscometers

Blood samples on EDTA were also collected for the assessment of blood viscosity. The collection of blood samples was performed according to the ICSH guide (8), and haemorheological measurements were performed within 4 hours of blood collection.

Viscosity measurements were carried out at a constant temperature of 37 degrees Celsius using an organ bath. The viscometer has been calibrated according to the user manual. Calibration and proper operation were checked by measuring the viscosity of the standard solution for both Newtonian and non-Newtonian fluids.

Statistical analysis

All data was then included in a database made in Microsoft Excel and processed using SPSS for Windows v. 20.0. The descriptive data was presented as average +/- DS (standard deviation)

Results

The study protocol included the following data for the group of patients with chronic renal disease in diabetes: patient age, sex, background, type of therapy administered, degree of metabolic control and morbid associations within the demographic characteristics. Important haematological parameters, parameters of renal impairment as well as parameters of important glucidic metabolism have been observed regarding their influence on the rheological characteristics of the blood

The demographic and biological characteristics of the patients are presented in table no.1 and we can see that there are no significant differences in gender and age distribution, but the levels of glycated hemoglobin and creatinine and GFR were significantly different in the three groups.

Blood viscosity at different shear rates was measured, from 18.8 sec -1 to a rate of 788 sec-1 and the observations were made on both the total lot and the three different batches.

Another benefit of the viscosimeter would be that at high shear rates, blood viscosity measurements reflect red cell deformability, because erythrocytes become ellipsoid rotation.

At low shear rates, viscosity measurements on autologous plasma erythrocyte suspensions will reflect erythrocyte roller formation, which is directly proportional to the plasma concentration of high molecular weight proteins such as fibrinogen, a protein that has a very high ratio of friction and the rheological effect of these plasma proteins can be evaluated more easily by determining plasma viscosity.

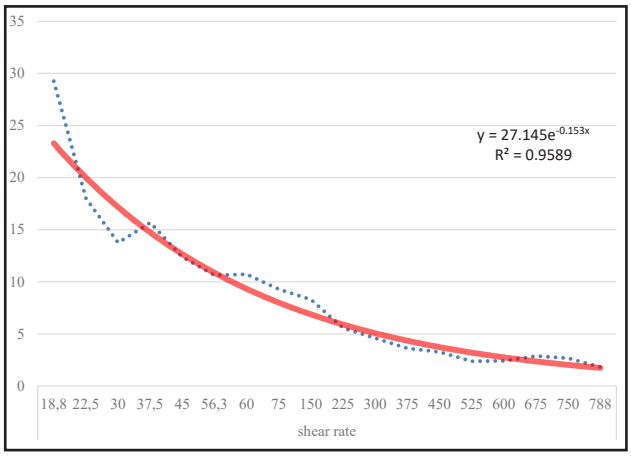

Figure 2 Viscosity of blood in patients enrolled in the study

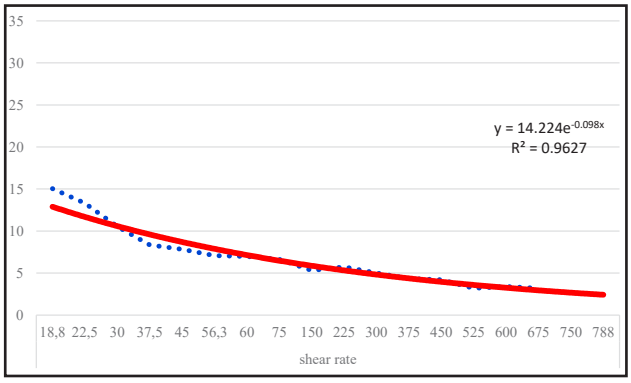

Figure 3 Viscosity of blood in patients in lot no. 1 without renal impairment or mild renal impairment

Table I. Demographic and Biological Characteristics

Demographic and Biological Characteristics	VALUES lot 1 No= 10	VALUES lot 2No= 18	VALUES lot 3 No=14
Age, average +/- SD (yrs) (min-max)	66.2 +/- 6.57	65.77+/-9.33	67.71+/-7.11
Men (no., %)	2 (20%)	8 (44,4%)	6 (42.85%)
Women (no., %)	8 (80%)	10 (55.6%)	8 (57.15%)
Women's report: men	8/2 (4)	10/8 (1.25)	8/6 (1.33)
Urban / rural background (no,%)	6 /4 (60%)	16/2 (88.8%)	14/0 (100%)
Hb, average +/-SD (g/dL)	14.5+/-1.687	13.13+/-1.009	9.54+/-2.01
Ht, average+/-SD (%)	44.28+/-3.86	39.29+/-2.39	28.47+/-6.51
CHEM, average +/-SD (%)	33.74+/-1.63	33.4+/-0.75	33+/1.77
MCV, average +/- SD (fL)	88.2+/-2.43	90.03+/-6.08	90.21+/3.6
ESR, average +/- SD (mm/h)	16.6+/-8.47	24.55+/-13.45	57.28+/-27.25
Fibrinogen, average +/-SD (mg/dl)	446.6+/-72.78	420.2+/-120.8	651.9+/-53.32
Creatinine, average +/-SD (mg/dL)	0.92+/-0.18	1.61+/-0.47	3.74+/-1.48
eGFR, average +/-SD (ml/min/1.73m2)	71.28+/-13.71	46.81+/-9.04	19.28+/-5.64
Glucose, average +/-SD (mg/dL)	158+/-39.53	159.55+/-28.89	172.28+/-41.17
HbA1c +/-SD (%)	6.8+/-0.6	7.92+/-1.18	9.31+/-2.14

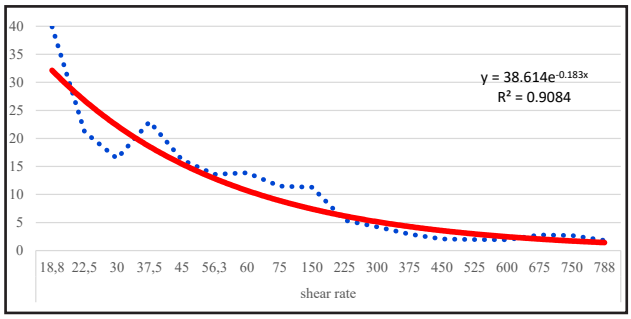

Figure 4 Viscosity of blood in patients in lot no. 3 with severe renal impairment

It is noticeable in patients with end-stage renal disease (ESRD) that there is low blood viscosity especially at high shear rates associated with anemia secondary to this condition, and there is also a low shear force (9-11) and this anomaly is associated with external arterial remodeling, increased arterial stiffness and reduced flow due to local vasodilation (10-12).

Increase in shear force after correction of anemia was associated with reduced arterial stiffness and improved vasodilator mediated flux (10-12).

Table II. Correlation between viscosity of blood and values of glycosylated hemoglobin

Viscosity value according to shear rate	Corelation with HbA1c lot 1	Corelation with HbA1c lot 2	Corelation with HbA1c lot 3
30	p = 0.021	p = 0.12	p = 0.21
225	p = 0.20	p = 0.0001	p = 0.04
300	p = 0.02	p < 0.0001	p = 0.002
375	p = 0.002	p < 0.0001	p < 0.0001
450	P = 0.0003	p < 0.0001	P = 0.0001

Statistically significant correlations between HbA1c value and blood viscosity have been observed, especially at shear rates over 200 s-1 especially in groups 2 and 3 of patients with moderate and severe renal impairment, but also a poor glycemic control expressed both glycosylated hemoglobin and glucose values. The viscosity at shear rates over 100 sec-1 is influenced by the ability of erythrocytes to deform in blood vessels with small and very small diameters.

Table III Correlation between viscosity of the blood and values of serum glucose

Viscosity value according to shear rate	Corelation with values of glucose lot 1	Corelația cu valorile glicemiei lot 2	Corelația cu valorile glicemiei lot 3
30	p = 0.001	p < 0.0001	p < 0.0001
225	p = 0.00098	p < 0.0001	p < 0.0001
300	p = 0.00097	p < 0.0001	p < 0.0001
375	p = 0.00095	p < 0.0001	p < 0.0001
450	p = 0.00095	p < 0.0001	p < 0.0001

Discussion

Blood viscosity is an important determinant of local flow characteristics. Blood has a thinning phenomenon due to shear stress: its viscosity decreases exponentially correlated with increased shear rate. The effect caused by changes in blood viscosity in patients with diabetic nephropathy is not yet sufficiently clarified.

Vekasi and all. in the study (11) reported that elevated blood glucose levels in diabetic patients despite antidiabetic medication can lead to hemorrhoidal disorders that will cause a disruption to microcirculation. These elevated blood glucose levels over a long period of time causes ischemia in the various tissues (12-14), which is the main reason that leads to the formation of new capillaries, leading to the occurrence of retinopathy and nephropathy.

Glycosylation of hemoglobin as well as increased blood glucose levels tend to primarily affect the properties of erythrocytes, lowering red cell flexibility and increasing erythrocyte aggregability, which is responsible for increased blood viscosity (15).

Conclusions

Blood viscosity was increased in patients with major organ complications but not at high shear rates in patients with early complications, closely correlated with decreased glycemic control expressed by glycosylated hemoglobin levels.

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