Medical prevention through mathematical models: assessing the evolution of diabetic complications

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Abstract. The aim of the study was to evaluate hemorheological changes in diabetic patients with renal complications, also to observe the influence of biological parameters in blood viscosity and to determine the progression of disease by using a mathematical model with multiple linear regression equation in the intent of limiting the evolution of diabetic nephropathy.

The study compared rheological and biological measurements in 21 patients with different stages of diabetic nephropathy, controlled with a subset of 18 healthy subjects.

Progressive inclusion of the different rheological and biological parameters resulted into a mathematical model according with their statistically significant relevance and renal involvement.

Results demonstrated a strong dependency of at least five parameters that can be modifiable through proper therapy and diet and may influence the viscosity of blood and, implicitly, the micro-vascular complications of diabetes mellitus.

1. Introduction

Diabetes mellitus tends to become „pandemic” in this century and along with it, the microvascular complications are more frequent. Any possibility to identify and prevent the progression of microvascular changes may be of extreme utility. According to PREDATORR [1] in 2014, from 3000 subjects in multiple national centers, in Romania the incidence of diabetes mellitus was estimated at 11.6% for ages ranging between 20 to 79 years.

Hemorheology is a branch of medical science that analyzes macroscopically, microscopically and molecularly the flow properties of blood components.

Diabetic nephropathy represents one of the major complications of diabetes mellitus and using the renal parameters into an mathematical model may help diagnosis and prevention of disease.

Also, the indirect methods of determining rheological parameters, mainly the evaluation of blood viscosity, are applicable more and more often in practice. Why not to establish the best equation of preventing renal complications?

2. Material and method

In the study were included 21 patients with diabetes mellitus type 2, with different stages of renal involvement, selected from the database of primary care physician, from the Nephrology Department in Central Emergency Hospital „Sf Apostol Andrei” Constanța, Romania and also from the „DIAVERUM” Nephrology and Dialysis Center, Constanța, Romania. 18 subjects in control group were selected from general population, were properly informed and signed the written consent for enrolling in the study.

The evaluation of blood viscosity was performed by using the Brookfield DV-II + rotational viscometer, with a cone spindle of 40. Blood samples (2 ml) were taken on EDTA and have been executed in the first two hours after preivation.

Mean age in diabetic patients was 66.52±7.71 years, and in controls 51±4.56 years.
Table no. 1 Biological parameters in patients with diabetes mellitus vs. controls

| Biological parameter          | Mean values (DM) +/- SD | Mean values (controls) +/- SD |
|------------------------------|-------------------------|-------------------------------|
| Hb(g/dL)                     | 12.26+/- 2.52           | 14.79+/- 0.74                |
| Ht(%)                        | 36.50+/- 10.90          | 45.06+/- 1.70                |
| ESR(mm/h)                    | 34.10+/- 16.07          | 8.5+/- 3.05                  |
| BUN(mg/dL)                   | 66.05+/- 21.38          | 33.38+/- 5.41                |
| Serum Creatinine(mg/dL)      | 2.21+/- 1.51            | 0.85+/- 0.10                 |
| GFR (ml/min/1.73m²)          | 43.46+/- 17.97          | 104.55+/- 15.87              |
| FBS(mg/dL)                   | 163.42+/- 34.59         | 90.25+/- 5.67                |
| Fibrinogen(mg/dL)            | 503.70+/- 139.20        | 297.22+/- 53.70              |
| WBC(elem/mm³)                | 7713.01+/- 3274.20      | 6603.33+/- 1382.10           |
| PLT(elem/mm³)                | 221285.71+/- 48111.47   | 282500+/- 42973.65           |

DM – diabetes mellitus; Hb – haemoglobin; Ht – heamatocrit; ESR – erithrocyte sedimentation rate; BUN – blood urea nitrogen; GFR – glomerular filtration rate; FBS – fasting blood sugar; WBC – white blood cells count; PLT – platelet count

Initial analysis (Table no.1) was performed in order to determine which of the 11 parameters (shear stress, haematocrit, fibrinogen, WBC, platelets, Hb, glycaemia, BUN, ESR, creatinine or glomerular filtration rate) present a sufficiently statistically significant correlation that indicates how much this independent variable influences the determined blood viscosity at a sheare rate of 60 sec⁻¹ (vs8 in table 2).

Table no.2 Blood viscosity in patients with DM vs. controls

| Studied group | Viscosity at sr 60sec⁻¹ |
|---------------|-------------------------|
| DM            | 9.44+/- 3.37            |
| Controls      | 5.94+/- 1.74            |
| p value       | 0.32                    |

DM – diabetes mellitus;

After these measurements, every variable (parameter) was analyzed separatelly with blood viscosity value, in order to establish wether there is a direct linear correlation with the data obtained from the 21 patients and to identify the exact value of multiple correlation coeficient (to be included must be higher than 0.1).

Anaylsis was performed by Excel statistical functions and MATLAB programming.

3. Results

All measured parameters were correlated sequentially with viscosity values.

![Figure no.1 Correlation between shear stress and blood viscosity(Excel)](image)
Analytical expression for the equation of regression for shear stress is:

\[ \vartheta_{blood_{vs8}} = 0.0836 + 1.5730 \gamma_{shear\_stress8} \]

with \( R^2 = 0.964 \)

From initial analysis, it was depicted the dependency of blood viscosity on the following parameters (out of initial 11 – table no.3): shear stress, fibrinogen, BUN, ESR and GFR.

Table no. 3 Correlation level of significance for different biological parameters in patients with diabetic nephropathy

| Biological parameters | Correlation coefficient - \( R^2 \) |
|-----------------------|----------------------------------|
| Ht                    | 0.0004                           |
| Fibrinogen            | 0.1113                           |
| WBC                   | 0.0295                           |
| PLT                   | 0.0154                           |
| Hg                    | 0.0032                           |
| FBS                   | 0.0174                           |
| BUN                   | 0.1923                           |
| ESR                   | 0.1800                           |
| Creatinin             | 0.0060                           |
| GFR                   | 0.1121                           |

Hb – haemoglobin; Ht – haematocrit; ESR – erythrocyte sedimentation rate; BUN – blood urea nitrogen; GFR – glomerular filtration rate; FBS – fasting blood sugar; WBC – white blood cells count; PLT – platelet count

A multilinear regression analysis was performed in correlation with blood viscosity.

The second stage of analysis expressed the blood viscosity (\( \vartheta_{blood_{vs8}} \) (cP) depending on two or more variables

After introducing independent variables, the results are as follows:
a) With two independent variables (shear stress and fibrinogen), the regression equation is:
\[ \vartheta_{\text{blood vs}} = -1.4254 + 1.5476 \gamma_{\text{shear stress}} + 3.29 \times 10^{-3} F_{\text{Fibrin vs}} \]

The value of the value of multiple determination coefficient is \( R^2 = 0.9668 \) and the value of multiple correlation coefficient is \( R = 0.9832 \).

| Regression coefficients | Standard error |
|-------------------------|--------------|
| Intercept (variables)   | -1.42544617  | 1.347303  |
| x1 Shear stress         | 1.547676513  | 0.071849  |
| x3 Fibrinogen           | 0.003294961  | 0.002696  |

b) With three independent variables (shear stress, fibrinogen and BUN), the regression equation is:
\[ \vartheta_{\text{blood vs}} = -1.194 + 1.533 \gamma_{\text{shear stress}} + 1.969 \times 10^{-3} F_{\text{Fibrin vs}} + 7.92 \times 10^{-3} B_{\text{BUN vs}} \]

The value of the value of multiple determination coefficient is \( R^2 = 0.9676 \) and the value of multiple correlation coefficient \( R = 0.9836 \).

| Regression coefficients | Standard error |
|-------------------------|--------------|
| Intercept (variables)   | -1.194095955 | 1.411731592|
| x1 Shear stress         | 1.533030445  | 0.076207623|
| x2 Fibrinogen           | 0.001969934  | 0.003382267|
| x8 BUN                  | 0.007920375  | 0.011863725|

Statistical regression

|                          |                |
|--------------------------|----------------|
| \( R \) – Multiple correlation coefficient | 0.983265302   |
| \( R^2 \) – Multiple determination coefficient | 0.966810654   |
| \( R^2_c \) – Corrected multiple determination coefficient | 0.963122949   |
| Standard error           | 1.607441457   |
| No. (patients)           | 21             |

|                          |                |
|--------------------------|----------------|
| \( R \) – Multiple correlation coefficient | 0.983696387   |
| \( R^2 \) – Multiple determination coefficient | 0.967658583   |
| \( R^2_c \) – Corrected multiple determination coefficient | 0.961951274   |
| Standard error           | 1.63277797    |
| No. (patients)           | 21             |
c) With four independent variables (shear stress, fibrinogen, BUN and ESR), the regression equation is:

\[ \vartheta_{\text{blood vs 8}} = -0.49 + 1.518 \gamma_{\text{shear stress 8}} - 5.78 \times 10^{-4} \text{FIBRIN vs 8} + 4.21 \times 10^{-3} \text{BUN vs 8} + 2.71 \times 10^{-2} \text{ESR vs 8} \]

The value of the value of multiple determination coefficient is \( R^2 = 0.9705 \) and the value of multiple correlation coefficient \( R = 0.9851 \).

| Regression coefficients | Standard error |
|-------------------------|----------------|
| Interception (variables) | -0.490095116 | 1.495766 |
| \( x_1 \) Shear stress | 1.518246742 | 0.075826 |
| \( x_3 \) Fibrinogen | -0.000578081 | 0.00389 |
| \( x_8 \) BUN | 0.004210632 | 0.012027 |
| \( x_9 \) ESR | 0.027179719 | 0.021543 |

Statistical regression

- \( R \) – Multiple correlation coefficient: 0.9851
- \( R^2 \) – Multiple determination coefficient: 0.9705
- \( R^2_c \) – Corrected multiple determination coefficient: 0.9632
- Standard error: 1.605081748
- No. (patients): 21

d) With five independent variables (shear stress, fibrinogen, BUN ,ESR and GFR ), the regression equation is:

\[ \vartheta_{\text{blood vs 8}} = -2.99 + 1.519 \gamma_{\text{shear stress 8}} - 9.339 \times 10^{-4} \text{FIBRIN vs 8} + 9.92 \times 10^{-3} \text{BUN vs 8} + 3.13 \times 10^{-2} \text{ESR vs 8} + 2.808 \times 10^{-2} \text{GFR vs 8} \]

The value of the value of multiple determination coefficient is \( R^2 = 0.9726 \) and the value of multiple correlation coefficient \( R = 0.9862 \).

| Regression coefficients | Standard error |
|-------------------------|----------------|
| Interception (variables) | -2.996807507 | 2.786167 |
| \( x_1 \) Shear stress | 1.519461142 | 0.07552 |
| \( x_3 \) Fibrinogen | 0.000933911 | 0.004126 |
| \( x_8 \) BUN | 0.00992479 | 0.013125 |
| \( x_9 \) ESR | 0.031341773 | 0.021807 |
4. Discussions

Chronic consequences of diabetes mellitus are translated into chronic impairment of microcirculation and the development of vascular complications. The results of former studies sustain the changes in the rheological parameters as a potential indicator of the progression of diabetic nephropathy, but these results are few and incomplete until now regarding the pathogenic mechanism.

Rheological changes associated with Diabetes mellitus may contribute to the reduction in renal perfusion leading to the development of micro vascular complications. Also, elevation in blood viscosity could represent an independent risk factor for diabetes mellitus, being suggested that it leads to aggravation of insulin resistance.

A simple way to interpret the rheological parameters is based on the principle that states that viscosity represents in fact a global evaluation in of the energy dissipation considering the main features of erythrocyte: deformability and aggregability. In order to explain the viscosity of the blood we can accept that it represents the opposite of blood fluidity, and any impairment may lead to vascular complications. It is accepted the fact that haematocrit is influencing the blood flow and blood viscosity in microcirculation.

Former studies are demonstrating an increase in blood viscosity in diabetic patients.

At low shear rates, as in our results, blood viscosity is determined mainly by erythrocyte aggregability and this process is conditioned by haematocrit and plasma protein levels [2].

The importance of determining blood viscosity was demonstrated also in ARIC study related to the risk of developing diabetes in normoglycaemic subjects [3].

An increased value of plasma fibrinogen is related to a concurrent increased force of disaggregation in erythrocytes, determining an increase in the blood viscosity at low shear rates. This fact allows the value of fibrinogen to be considered today a marker in the evolution of diabetic nephropathy, but also for other complications determined by the micro vascular changes [4-6]. An increased fibrinogen will determine an increase in the disaggregation force associated with reduced deformability of red blood cells [7].

An observational study in US that was made by data collected in between 1999 and 2008 on 50162 patients, used an indirect method of determination for blood viscosity and correlated the values of creatinine, glicaemia and lipid profile with the increased values of blood viscosity. Results showed high viscosity in 4% of patients with hyperglicaemia and hyperlipoproteinemia, and lower in patients with increased creatinine levels, the study exposing the association with severe renal impairment, especially for end stage renal disease (ESRD) [8].

Our study is presenting increased values for both blood viscosity and renal impairment markers in patients with diabetes mellitus compared with controls.

The study intended to develop a mathematical relationship based on multiple linear regressions by using biological parameters like haematocrit, glicaemia or fibrinogen in order to evaluate the evolution of changes into blood viscosity. Those parameters were included one by one up to the maximal statistical relevance.

| Parameter                      | Value       |
|--------------------------------|-------------|
| $R$ – Multiple correlation coefficient | 0.986230914 |
| $R^2$ – Multiple determination coefficient | 0.972651415 |
| $R^2_c$ – Corrected multiple determination coefficient | 0.96353522 |
| Standard error                 | 1.598430903 |
| No. (patients)                 | 21          |
The development of such regression models is offering a predictable prognostic tool in the evolution of diabetic patients with renal impairment in the attempt of reducing the vascular complications.

5. Conclusions

Statistical analysis shows a strong dependency in between five measured parameters: shear stress, fibrinogen, blood urea nitrogen, erythrocyte sedimentation rate and glomerular filtration rate, as independent variables, and blood viscosity. The mathematical model might be a real benefit in the diagnosis of diabetic nephropathy, due to the possibility of correction by proper therapy and diet. This is representing a real benefit into the improvement of the quality of life in diabetic patients by reducing the rate of progression for these severe complications.

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