

PREDICTIVE VALUE OF BLOOD GLUCOSE RANGE FOR ONSET OF COMPLICATIONS IN PATIENTS WITH DIABETES MELLITUS TYPE 1

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Abstract

Background and aims: to develop a prognostic mathematical model for risk of microangiopathy in patients with diabetes mellitus type 1 (T1DM). **Materials and methods:** 62 T1DM patients were divided into 2 groups according to HbA1c level: group 1 (n=18) with HbA1c \leq 7.0% and group 2 (n=44) with HbA1c $>$ of 7.0%. HbA1c, C-peptide, blood creatinine, estimated glomerular filtration rate (eGFR) CKD-EPI, first morning urinary albumin excretion (AU) were determined. Blood glucose levels were conducted by CGMS (Continuous Glucose Monitoring System). All patients were followed for 3 months. Rank correlation method was used. **Results:** We established the direct correlation between HbA1c the AU level $\rho=0.29$ ($p<0.016$) at the beginning and $\rho=0.4$ ($p=0.021$) after 3 months. AU level has a direct correlation with blood glucose range, at the beginning $\rho=0.51$ ($p<0.001$) and after 3 months $\rho=0.48$ ($p=0.004$) visits. We made the mathematical description of this dependence. Each additional unit of blood glucose range is accompanied by increasing an average level AU level by 0.4816 mg/l. **Conclusion:** our mathematical equation of dependence between AU level and blood glucose range gives the opportunities to predict diabetic kidney disease progression in T1DM patients.


key words: diabetes, blood glucose range, albuminuria

Background and aims

Today diabetes mellitus (DM) is one of the leading medical and social problems. The World Health Organization (WHO) informs that the number of patients with DM is increasing annually. Presently, there are about 422 million people with diabetes in the world [1]. The overall incidence of DM has almost doubled since 1980, rising from 4.7% to 8.5%. The International Diabetes Federation (IDF)

identifies that the total number of DM patients will reach 629 million by 2045 [2]. Patients with type 1 diabetes mellitus (T1DM) account for 5-10% of the total cases of DM. The prevalence of T1DM in children under 15 years is increasing all over the world with the average annual growth about 3%. Annually, 132600 new medical cases of T1DM are registered among young people under the age of 20 years old [2,3].

Microangiopathy is one of the major complications of T1DM. The pathophysiology of

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diabetic microangiopathy is multifactorial and caused by hyperglycemia. There are a few pathological processes, which it forms microvascular complications: non-enzymatic glycation of proteins, the polyol pathway activation, glucose toxicity and the violation of glycosaminoglycan exchange [4]. Chronic hyperglycemia promotes endothelial dysfunction, which leads to formation of chronic diabetic complications [5,6]. Diabetic microangiopathy is the main cause of the patient's disability and mortality. That's why diabetic microangiopathy defines the disease course and prognosis [5,7].

The aim of the study: to develop a prognostic mathematical model for risk of microangiopathy, a in patients with type 1 DM.

Materials and methods

62 T1DM patients were enrolled in this study, including 25 men (40.32%) and women - 37 (57.68%). Average age was 31.5 (24.0; 39.0). The study was conducted in the Endocrinology Department of University Clinic of «Dnepropetrovsk Medical Academy», 2016-2017. The duration of the disease was 11.0 (5.0; 18.0) years and the body mass index (BMI) 23.06 (20.81; 24.08) kg/m². All patients used basic-bolus insulin therapy with the insulin daily dose 45 (35.0; 58.0) units.

Exclusion criteria: Type 2 DM; diabetic ketoacidosis at the moment of inclusion; secondary DM; body mass index (BMI) > 40 kg/m²; diabetic proliferative retinopathy; chronic kidney disease IIIB - V; diabetic foot (II Wagner class and above); heart failure III / IV by the New York Heart Association (NYHA); congenital and acquired heart disease; acute coronary syndrome, acute ischemic stroke and transient ischemic attack; exacerbation of accompanying chronic diseases; acute illness; pregnancy.

All the patients signed informed consent form, approved by the local Ethics Committee. The procedures performed in study involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

The diagnosis of T1DM was made according to American Diabetes Association (ADA) criteria - 2016 [8].

The C-peptide, HbA1c, blood creatinine, the first morning urinary albumin (AU) were determined at the beginning and 3 months after treatment modification. C-peptide was determined on the electrochemiluminescence automatic immunochemical analyzer COBAS e 411, Roche Diagnostics GmbH & Hitachi, Japan, 2012. The blood creatinine level, HbA1c and AU were determined using automatic biochemical analyzer SAPPHERE 400, Tokio Boeki, Japan, 2009. eGFR was calculated according to CKD-EPI formula. Long-term monitoring of blood glucose levels was conducted by using the system CGMS (Continuous Glucose Monitoring System, Medtronic MiniMed, USA). This system detects electrical signals every 10 seconds and transforming them in glucose values every 5 minutes. Hypoglycemia was considered as an episode of lower blood glucose level less than 3.9 mmol/l according to ADA criteria [8]. The maximum and minimum blood glucose levels and the blood glucose range (maximum minus minimum blood glucose values due to CGMS), were considered.

Patients were divided into 2 groups according to the level HbA1c: Group 1-HbA1c ≤7.0 % (n=18), Group 2 – HbA1c>7.0 % (n=44). 10 *healthy age- and sex-matched controls were included* in this study. The *treatment modification* was performed in patients with poor glucose control (HbA1c higher, than individual target level and/or frequent

hypoglycemic conditions). It included changes of insulin doses, treatment regimen, lifestyle modification and regular self-monitoring of blood glucose.

Statistical analysis

The data were analyzed using Microsoft Excel (Office Home Business) with add-on AtteStat and the software STATISTICA 6.1 (StatSoftInc.). The data were described by median and quarterly ranges (Me (25%; 75%). The Spearman rank correlation coefficient (ρ) was calculated. Correlation coefficient in range $0.7 \leq |\rho| < 1$ shows the strong correlation, in range $0.3 \leq |\rho| < 0.7$ shows the average correlation, and in range $0 < |\rho| < 0.3$ – a weak correlation.

Results

The groups of patients were compared by age and sex, duration of the disease, main anthropometric indexes, insulin daily dose, eGFR and the AU level. In group 1 the average HbA1c was 6.85 (6.65, 7) %, in group 2 – 10.95 (9.4, 12) %, in control group – 4.35 (4.05; 4.7) %. The moderately increased AU was determined in 27.78% patients in group 1 and 54.55% patients in group 2. The severely increased albuminuria AU was defined in 5.56% patients in group 1 and 4.55% patients in group 2.

T1DM patients had significantly higher HbA1c, creatinine, eGFR, AU levels, and significant lower C-peptide level ($p < 0.001$) compared to control. These trends are stored after 3 months (Table 1).

Table 1. Laboratory data in study groups (Median and interquartile range - Me (25%; 75%).

Parameters	Group 1 (n=18)	Group 2 (n=44)	T1DM (n=62)	Control group (n=10)	Comparison between groups	
					<i>p</i>	<i>p_{0-κ}</i>
HbA1c, % beginning	6.85 (6.65; 7)	10.95 (9.4; 12)	9.8 (7.4; 11.2)	4.35 (4.05; 4.7)	<i>p</i> < 0.001 <i>p_{1-κ}</i> = 0.398 <i>p_{2-κ}</i> < 0.001 <i>p₁₋₂</i> < 0.001	< 0.001
HbA1c, % after 3 months	7 (6.7; 8.08)	9.2 (7.6; 10)	8.5 (7; 9.7)		<i>p</i> < 0.001 <i>p_{1-κ}</i> = 0.133 <i>p_{2-κ}</i> < 0.001 <i>p₁₋₂</i> = 0.117	< 0.001
<i>p</i> between visits. *	0.173	0.081	0.104	-	-	-
C-peptide ng/ml	0.02 (0.01; 0.65)	0.01 (0.01; 0.1)	0.01 (0.01; 0.15)	2.85 (2.6; 3.45)	<i>p</i> < 0.001 <i>p_{1-κ}</i> = 0.002 <i>p_{2-κ}</i> < 0.001 <i>p₁₋₂</i> = 0.670	< 0.001
Creatinine, μmol / ml beginning	91.12 (83.06; 95.87)	96 (89.9; 103.97)	94.6 (86.12; 103.35)		68.5 (66.5; 84)	<i>p</i> < 0.001 <i>p_{1-κ}</i> = 0.033 <i>p_{2-κ}</i> < 0.001 <i>p₁₋₂</i> = 0.193
Creatinine, μmol / ml after 3 months	96 (94.91; 100.24)	91.16 (86.82; 99.05)	94.91 (88.99; 99.6)	<i>p</i> < 0.001 <i>p_{1-κ}</i> = 0.001 <i>p_{2-κ}</i> = 0.002 <i>p₁₋₂</i> = 0.735		< 0.001
<i>p</i> between visits *	0.237	0.686	0.882	-	-	-

Table 1. Continued.

Parameters	Group 1 (n=18)	Group 2 (n=44)	T1DM (n=62)	Control group (n=10)	Comparison between groups	
					<i>p</i>	<i>p</i> _{o-k}
eGFR , ml / min / 1.73 m ² beginning	79 (71; 86)	75 (66; 85)	76 (67; 85)	108,5 (105; 111)	<i>p</i> <0.001 <i>p</i> _{1-k} =0.003 <i>p</i> _{2-k} <0.001 <i>p</i> ₁₋₂ =1.000	<0.001
eGFR , ml / min / 1.73 m ² after 3 months	76 (65; 83)	74 (69; 80)	75 (69; 80)		<i>p</i> <0.001 <i>p</i> _{1-k} =0.005 <i>p</i> _{2-k} <0.001 <i>p</i> ₁₋₂ =1.000	<0.001
<i>p</i> between visits *	0.176	0.225	0.954	-	-	-
AU, mg/l beginning	23.45 (15.4; 38.9)	34.4 (16.8; 51.2)	30,3 (16.8; 44.7)	6.7 (5.5; 9.4)	<i>p</i> <0.001 <i>p</i> _{1-k} =0.006 <i>p</i> _{2-k} <0.001 <i>p</i> ₁₋₂ =0.881	<0.001
AU, mg/l after 3 months	20.9 (12.2; 31.6)	24 (19.9; 47.6)	22.8 (13,8; 43.7)		<i>p</i> <0.001 <i>p</i> _{1-k} =0.025 <i>p</i> _{2-k} <0.001 <i>p</i> ₁₋₂ =1.000	<0.001
<i>p</i> between visits. *	0.866	0.043	0.353	-	-	-

Notes. *p* – differences between groups according to the non-parametric dispersion analysis of Kruskal-Wallis (KW-H); aposteriori comparisons – according to the Dunn criteria, pairwise – by Mann-Whitney (U):

*p*_{1-k} – between group 1 and control group;

*p*_{2-k} – between group 2 and control group;

*r*_{o-k} – between the main group and the control group;

*p*₁₋₂ – between group 1 and group 2

*- *p* in the dynamics between the beginning and after 3 months according to the Wilcoxon test.

Due to CGMS, both groups separately and range compared with the control group. major groups generally have significantly higher (p<0.001). There were no statistically significant maximum glucose levels and blood glucose differences between groups (Table 2).

Table 2. Blood glucose levels in study groups, mmol/l (Median and interquartile range - Me (25%; 75%)).

Parameters	Group 1 (n=18)	Group 2 (n=44)	T1DM (n=62)	Control group (n=10)	Comparison between groups	
					<i>P</i>	<i>P</i> _{o-k}
Minimum blood glucose level, mmol/l beginning	4.2 (3.4; 4.7)	4.3 (2.2; 6.1)	4.3 (2.75; 5.15)	4.05 (3.95; 4.3)	<i>p</i> =0.967	0.879
Minimum blood glucose level, mmol/l after 3 months	4.7 (2,2; 6.2)	4.85 (3.6; 5.4)	4.8 (3.6; 5.4)		<i>p</i> =0.258	0.115
<i>p</i> between visits. *	0.671	0.139	0.326	-	-	-
Maximum blood glucose level, mmol/l beginning	13 (11; 17.5)	16.5 (12.6; 19.5)	15.75 (12.3; 18.95)	5,65 (5,3; 5,95)	<i>p</i> <0.001 <i>p</i> _{1-k} =0.005 <i>p</i> _{2-k} <0.001 <i>p</i> ₁₋₂ =0.191	<0.001

Table 2. Continued.

Parameters	Group 1 (n=18)	Group 2 (n=44)	T1DM (n=62)	Control group (n=10)	Comparison between groups	
					P	P _{o-k}
Maximum blood glucose level, mmol/l after 3 months	12.8 (10.2; 16)	14.8 (11.4; 16.4)	14.8 (11.4; 16.1)		p<0.001 p _{1-k} =0.006 p _{2-k} <0.001 p ₁₋₂ =0.694	<0.001
p between visits.*	0.866	0.139	0.106	-	-	-
Blood glucose range, mmol/l beginning	8.6 (6.4; 12.7)	10.35 (8.55; 13.65)	10 (7.4; 13.2)	1.55 (1.1; 1.85)	p<0.001 p _{1-k} =0.003 p _{2-k} <0.001 p ₁₋₂ =0.368	<0.001
Blood glucose range, mmol/l after 3 months	8.25 (6.3; 11.4)	10 (5.4; 12.5)	8.4 (5.4; 12.5)		p=0.001 p _{1-k} =0.020 p _{2-k} =0.001 p ₁₋₂ =0.811	<0.001
p between visits.*	0.327	0.085	0.054	-	-	-

Notes. p – differences between groups according to the non-parametric dispersion analysis of Kruskal-Wallis (KW-H); aposteriori comparisons – according to the Dunn criteria, pairwise – by Mann-Whitney (U):

p_{1-k} - between group 1 and control group;

p_{2-k} – between group 2 and control group;

r_{o-k} – between the main group and the control group;

p₁₋₂ – between group 1 and group 2

*- p in the dynamics between the beginning and after 3 months according to the Wilcoxon test

Table 3. Albuminuria Level (mg/l), depending on the presence of hypoglycemia (Median and interquartile range - Me (25%; 75%))

Visit	Group 1 (n=18)		Group 2 (n=44)		T1DM patients (n=62)	
	hypoglycemic episode		hypoglycemic episode		hypoglycemic episode	
	no (n=10)	yes (n=8)	no (n=25)	yes (n=19)	no (n=35)	yes (n=27)
Beginning	21,7 (12,12; 28,0)	33,25 (21,4; 66,18)	29,0 (16,5; 43,35)	36,33 (17,1; 60,6)	23,5 (15,4; 38,9)	36,33 (20,0; 60,6)
p between groups	0,143		0,282		0,079	
After 3 month	20,9 (13,8; 24,1)	20,25 (8,9; 31,6)	22,8 (19,9; 43,7)	28,3 (22,1; 51,8)	22,8 (13,8; 43,7)	28,3 (8,9; 51,8)
p between groups	0,846		0,844		0,976	

Notes. p – differences between groups according to Mann-Whitney test (U).

Initially the study groups did not differ by the frequency of hypoglycemia: 44.4% in group 1, 43.18 % in group 2 (p=0,798) and 43.55% of all patients with T1DM. There were no statistical differences between the groups in AU level depending on presence of hypoglycemic episodes ([Table 3](#)).

We confirmed the absence of correlation between the AU level and the presence of hypoglycemic episodes as well as the maximum glucose level using the rank correlation analysis (p>0.05).

In group 2 there was a tendency to decreasing of HbA1c level (p<0.1), which was

10.95 (9.4; 12) % at the beginning and 9.2 (7.6; 10) % after 3 months. At the same time, the level of AU significantly reduced from 34.4 (16.8; 51.2) mg/l at the beginning of the study till 24 (19.9; 47.6) mg/l after 3 months ($p = 0.043$) in the group with poor glucose control.

There were no statistically significant changes in the blood glucose levels and the blood glucose range in the dynamics between the beginning and after 3 months ($p > 0, 05$) (Table 2).

We established the direct correlation between HbA1c the AU level, using the rank correlation method, $\rho=0.29$ ($p < 0.016$) at the beginning and $\rho=0.4$ ($p=0.021$) after 3 months. The AU level has increased direct average correlation with maximum blood glucose level both at the beginning of the study and 3 months after the treatment modification: $\rho=0.37$ ($p=0,002$) and $\rho=0, 45$ ($p=0.009$) respectively. The trend of albuminuria level at the beginning and after 3 months performed in Figure 1.

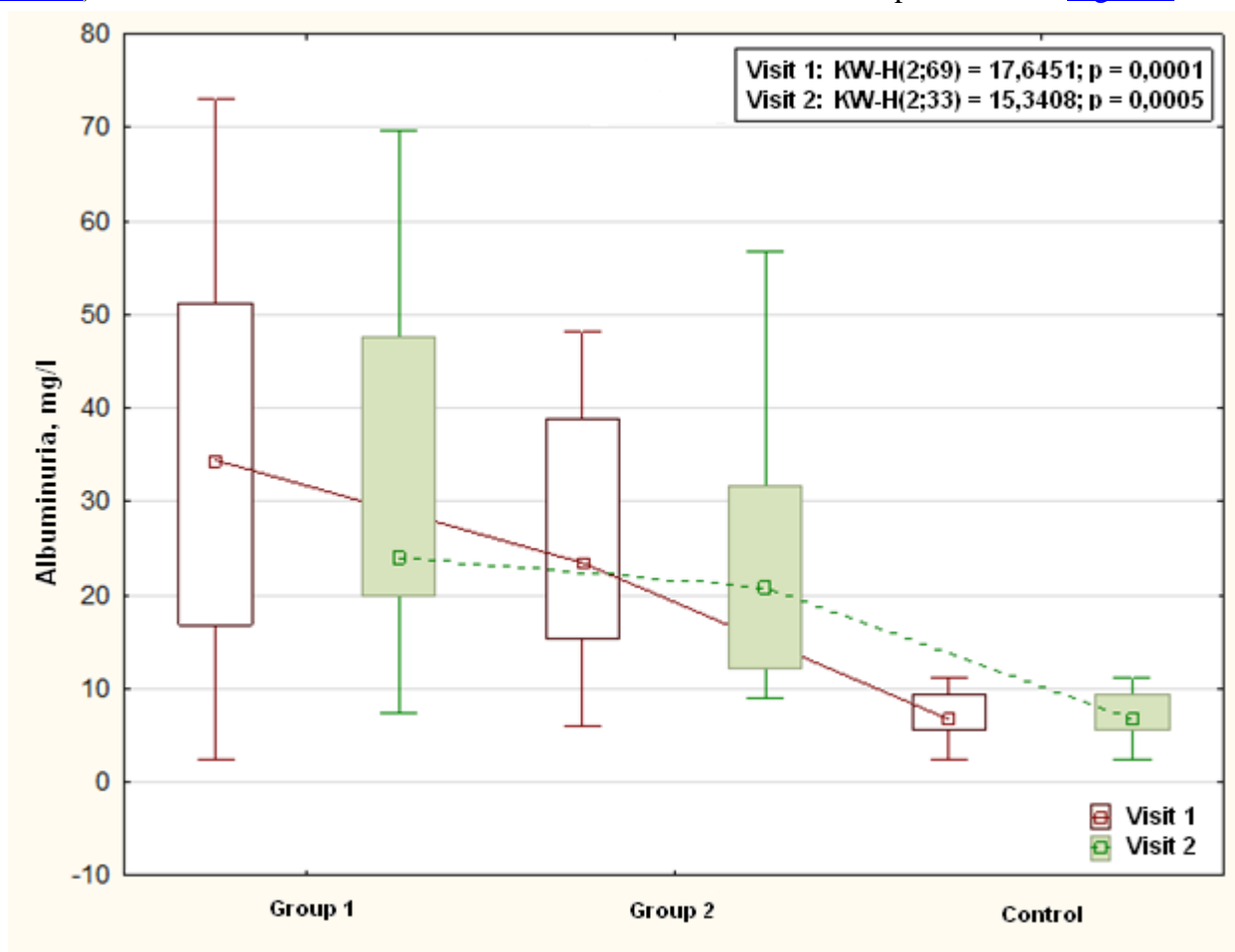


Fig. 1. The average level of albuminuria (mg/l) in the 1st and 2nd visits in study groups (median and quarterly ranges – Me (25%; 75%))

We estimated that AU level has a direct correlation with blood glucose range level, at the beginning $\rho=0.51$ ($p < 0,001$) and after 3 months $\rho=0,48$ ($p=0,004$).

We decided to make a mathematical description of this dependence. AU did not appear to have normal distribution, so original

data were transformed using an extension of the Box–Cox transformation with appropriate parameters.

We define the change in the AU level, depending on blood glucose range in T1DM patients, using simple linear regression analysis.

A linear regression line has an equation:

$$Y = a + bX, \quad (1),$$

Where Y is the predicted value of the dependent variable, a free term in equation: is the point where the line crosses the Y-axis.

an angular coefficient,

X –a predictive variable for the calculation of the corresponding value Y.

The model of the dependence between the AU level and blood glucose range level can be expressed by the equation:

$$Y = 3.7817 + 0.44816 \times X, \quad (2),$$

Where X means the difference between the maximum and minimum blood glucose level,
Y - is the predicted value of AU.

The angular coefficient $b = 0.4816$. It means, that each additional unit of blood glucose range is accompanied by increasing an average level AU level by 0.4816 mg/l.

The partial correlation coefficient and the determination index were calculated to assess the tightness of relations. Partial correlation

coefficient is 0.54 ($p < 0.001$); determination index is $r^2 = 28.86\%$. Consequently, 28.86% cases of blood glucose range change lead to increase AU level and also 28.86% cases of AU level change are occurring to blood glucose range change.

The remaining percentages of the Y variables are explained by the factors that can be neglected in this model.

The validity of the regression model was checked using Fisher's F criterion. The model can be defined as valuable, according to F-test ($F = 24.34$) ($p < 0.001$). Assessment of the regression models quality was performed using mean approximation error (mean deviation between calculated and actual values). The approximation error is 9.84% that is not higher than 15% so it is quite acceptable.

A scatter diagram of the relationship between the blood glucose range and the AU level in T1DM patients is shown in [Figure 2](#).

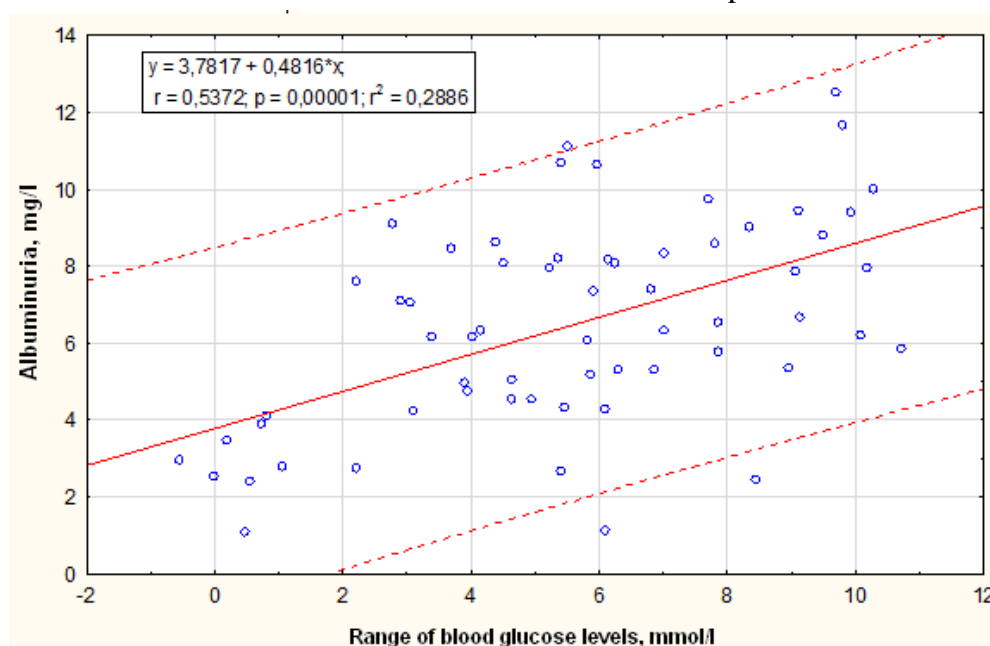


Fig. 2. Dependence between the blood glucose range and the level of albuminuria in T1DM patients.

Discussion

The results of our study confirm the glucose control effects on the onset and progression of microvascular complications. The Diabetes

Control and Complications Trial (DCCT) involved 1441 patients with T1DM from 1983 till 1983. Study results showed that intensive therapy reduced an average AU by 39%, and

expressed AU by 54%, the risk of proliferative retinopathy by 47% [9].

The Epidemiology of Diabetes Interventions and Complications (EDIC) study involved 96% of DCCT participants in 1994. Findings from EDIC demonstrated that early and intensive blood glucose control lowers risks of diabetic kidney disease (DKD) by 50% after 18 years and eye surgery for diabetic retinopathy by 48% after 17 years of DCCT completion [10,11].

The HbA1c variability was analyzed in DCCT and showed, that diabetic complications progression was estimated over 9 years. The definition of both HbA1c variability and the HbA1c level contributed more accurate prediction of microvascular complications development. Due to DCCT results, an increase HbA1c variability by 1% was associated with risks of retinopathy and DKD progression [9,12].

HbA1c is the gold standard to assess glucose control, but it does not involve glucose fluctuations. Glucose variability has been actively investigated after the introduction of continuous glucose monitors [9,13]. Although there was no confirmation of glucose variability effect on development and progression of diabetic complications. But some authors consider that determination of glucose variability is necessary because it's leading to endothelial dysfunction and angiopathy [14-16].

In recent years, a large number of mathematical methods of glucose variability evaluation have been developed. Each method has its own peculiarities but none of them currently can be considered as integrated GV

evaluation criteria. The estimation of GV had a number of problems in real clinical practice.

First of all, several indexes should be calculated for exact GV definitions.

Secondly, some GV parameters (MAGE, AUC, CONGA) specifically designed to evaluate GV using continuous glucose monitoring and appropriate software for this process [17].

We proposed the method for predicting onset and progression of diabetic microangiopathy in T1DM patients. It is not required any special software. The calculation may be performed using blood glucose self-monitoring data in a real clinical practice.

Conclusions

In the first place, in our study we defined that increasing range glucose level as well as hyperglycemia has impact on the onset of DM microvascular complication, as an example of DKD.

Secondly, we made a mathematical equation of dependence between AU level and blood glucose range using a simple linear regression analysis in T1DM patients that gives the opportunities to predict DKD progression in patients with T1DM.

Thirdly, the prediction of the onset and AU progression in T1DM patients can be used in clinical practice. It helps to identify the patients with high risks of DKD for early start of treatment and make prevention of DKD progression.

Conflicts of interest. No conflict of interest.

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