RELATIONSHIP OF VASCULAR COMPLICATIONS AND EXENATIDE THERAPY FAILURE IN TYPE 2 DIABETIC PATIENTS

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SUMMARY – Exenatide is an incretin mimetic that acts through glucagon-like peptide 1 receptor accepted as a successful novel glucose-lowering agent in type 2 diabetes. The aim of this study was to explore the possible predictive factors for exenatide efficacy among baseline characteristics of type 2 diabetic patients. We observed basic anthropometric measurements, laboratory findings and diabetic complications in ninety-one type 2 diabetic patients starting exenatide therapy. There were forty-six (50.5%) male and forty-five (49.5%) female patients, median age 58 (31-76) years, body mass index 38.95±4.35 kg/m^2, duration of diabetes 10 (1-30) years and HbA1c level 8.3±1.4%. Thirty (33%) patients stopped therapy because of glycemic dysregulation during 105 (21-390) days on therapy. These patients differed statistically significantly from those that continued therapy according to the following seven variables: higher fasting glucose blood concentration (11.5 mmol/L (5.6-20) *vs*. 10.2 mmol/L (5-19), higher serum creatinine concentration (93 μmol/L (44-149) *vs*. 72 μmol/L (44-124), more frequent diabetic complications including retinopathy (56.7% *vs*. 27.9%), chronic kidney disease (43.7% *vs*. 24.7%), coronary artery disease (53.3% *vs*. 31.1%) and peripheral artery disease (60% *vs*. 34.4%), and less often concomitant metformin and exenatide therapy (62% *vs*. 82%). Bivariate logistic regression identified peripheral artery disease, coronary artery disease, retinopathy, and chronic kidney disease as risk factors for glycemic dysregulation on exenatide therapy. We found reasonable to consider that a higher rate of microvascular and macrovascular complications may indicate failure of exenatide therapy in the majority of patients.

Key words: *Exenatide; Glucagon-like peptide 1; Diabetes mellitus, type 2; Vascular complications, diabetic*

Introduction

Because of the rising trend in its incidence and prevalence, diabetes is one of the most challenging health problems worldwide. According to the International Diabetes Federation, 366 million people had diabetes in 2011 (8.3% of the general population) and by the year 2030 it will have risen to 552 million (9.9% of the population)[1]. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of these numbers. The progressive nature of the disease leads to the development of micro- and macrovascular complications that are the main cause of comorbidities, which at long term result into enormous economic costs[2]. Although several classes of antidiabetic drugs are currently available, less than 50% of T2DM patients achieve and maintain glycosylated hemoglobin (HbA1c) <7% and only ~15% achieve target levels of glycemia, lipidemia and blood pressure together[3]. This may be due to the fact that the mechanisms of action of most antidiabetic agents are not based on reversal

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of the main pathogenic disturbances of the disease, i.e. the triumvirate of insulin resistance in muscle and liver and pancreatic β cell failure[4,5]. Additionally, new findings suggest that adipose tissue, gastrointestinal tract, pancreatic α cells, kidney and brain together play an important role in the pathophysiological mechanism of T2DM progression[6]. Because of these facts, innovative approaches to the treatment are constantly being investigated and the incretin system compounds are currently the newest class of glucose lowering agents. The incretin mimetic exenatide was introduced in clinical practice several years ago and many experimental studies have shown that it might overcome previous therapy limitations acting through several different pathways[7]. Exenatide is a synthetic peptide that shares 53% of amino acid sequence with glucagon-like peptide 1 (GLP-1), the incretin the impaired effect of which was found to be related to many pathophysiological abnormalities in T2DM[8,9]. It acts through GLP-1 receptor that is expressed in the brain, heart, pancreas, skeletal muscle, adipose tissue and liver in different forms[10]. According to several clinical trial based outcomes, exenatide increases the early and late phases of insulin secretion resulting in normalization of fasting and postprandial glycemia. Additionally, exenatide enhances insulin sensitivity, delays gastric emptying resulting in satiety and reduces food intake, which leads to weight loss, improves fasting lipid profile, lowers blood pressure and has a cardioprotective effect[11]. These data suggest promising results in the future of T2DM metabolic control management. However, it has been noticed that every clinical study with exenatide has a certain number of dropouts due to hyperglycemia[12-14]. This advises that not all T2DM patients are suitable for this type of glucoregulation regimen. We decided to perform an open-label observational study in order to determine which basic factors may help us predict exenatide non-responders, i.e. T2DM patients whose blood glucose levels will not be adequately regulated on exenatide therapy.

Patients and Methods

Study protocol

This was a single-center open-label observational study performed at Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Zagreb, Croatia. The primary objective of the study was comparison of baseline characteristics of two groups of T2DM patients: those who achieved normalization of glycemia following their first injectable glucose-lowering therapy with exenatide and those who did not. Exenatide was added to each patient's current therapy regimen, so at study entry patients could be taking any oral antidiabetic agent. Exenatide was started at a 5-μg twice daily dose and increased to 10-μg twice daily, if needed. Daily glucose monitoring was required. Adverse events were assessed during hospital stay at therapy initiation or at each outpatient visit using a close-ended questionnaire. All patients gave their written informed consent before study entry.

Study participants

During the period of 14 months, i.e. from June 2011 to August 2012, we studied 91 patients selected according to strict inclusion and exclusion criteria, out of the 93 patients who had started exenatide therapy. Inclusion criteria were history of T2DM, HbA1c >7.5%, body mass index (BMI) >35 kg/m^2, glomerular filtration rate ≥30 mL/min, absence of gallbladder stones and recent pancreatitis episode, and exenatide as first injectable glucose-lowering therapy. Exclusion criteria were quitting exenatide therapy for any other reason except for glycemia dysregulation or gastrointestinal adverse events.

Study measurements

All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed in all study subjects. Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 minutes and expressed in mm Hg. Fasting venous blood samples were collected in the morning between 08:00 and 09:30 a.m. after an overnight fast for determination of complete blood count and biochemistry panel, lipid profile status, thyroid hormone status, serum creatinine, glycated hemoglobin (HbA1c), fasting C peptide and C peptide in 120", and insulin resistance determined by the Homeostasis Model Assessment (HOMA) index[15]. Status of diabetic complications (retinopathy, chronic kidney disease (CKD), periph-

eral and autonomic neuropathy, coronary artery disease (CAD) and peripheral artery disease) were established by specialist examination and additional diagnostic tests, if needed. CKD was defined as creatinine clearance <60 mg/mL/min or albuminuria >300 mg/24 h from at least two 24-h urine samples. CAD was defined as a history of myocardial infarction or electrocardiogram (ECG) evidence of ischemic heart disease. Follow-up evaluation was based on three point self-reported glucose profiles (morning, midday, evening) and seven point glucose profiles during the hospital stay and later at 3- and 6-month outpatient visits. Other variables were measured during the follow-up period and will be reported in additional papers.

Statistical analysis

Statistical evaluation of data was carried out using SPSS statistical package, version 17.0 for Windows. Baseline data were reported using descriptive statistics. Normality of distribution for continuous variables was analyzed using Kolmogorov-Smirnov test. Normally distributed variables were described with mean and standard deviation (SD), while variables that were not normally distributed were described with median, minimum and maximum. Nominal variables were reported with absolute numbers and percentages. To compare baseline characteristics of the two groups of patients we used parametric independent sample

Table 1. Demographic and physical examination data

	Disease control achieved	Disease control lost	p value, CI 95%
Exenatide therapy duration (days)	N=31 150 (2-420)	N=30 3 (1-392)	<0.001
Age (yrs)	N=61 56 (31-74)	N=30 62 (46-76)	0.110
Gender (F-female; M-male)	N=61 30 F (49.2%) 31 M (58.8%)	N=30 15 F (50%) 15 M (50%)	0.941
T2DM duration (yrs)	N=59 8 (0-30)	N=29 16 (4-24)	0.944
Weight (kg)	N=59 111 (86-168)	N=29 103 (78-148)	0.883
BMI (kg/m^2)	N=56 38 (31-53)	N=29 36 (30-49)	0.680
Waist circumference (cm)	N=39 120 (97-148)	N=29 118 (88-192)	0.925
Pulse rate (beats/min)	N=39 76 (64-107)	N=25 74 (60-120)	0.642
Systolic blood pressure (mm Hg)	N=57 140 (100-190)	N=28 140 (110-200)	0.810
Diastolic blood pressure (mm Hg)	N=57 65 (60-120)	N=28 82.5 (70-100)	0.229
Smoking	N=61 Yes 13 (8.2%) No 34 (73.8%) Data not available 14 (18%)	N=30 Yes 2 (6.7%) No 24 (80%) Data not available 4 (13.3%)	0.805
Alcohol use	N=61 Yes 13 (21.3%) No 34 (55.7%) Data not available 14 (23%)	N=30 Yes 6 (20%) No 18 (60%) Data not available 6 (20%)	0.923
History of hypertension	N=59 Yes 51 (86.4%) No 8 (13.1%)	N=30 Yes 28 (93.3%) No 2 (6.7%)	0.340
History of metabolic syndrome	N=61 Yes 60 (98.4%) No 1 (1.6%)	N=30 Yes 29 (96.7%) No 1 (3.3%)	0.612
History of disease complications	N=60 Yes 58 (96.7%) No 2 (3.3%)	N=30 Yes 30 (100%) No 0	0.312

t-test for continuous variables and its corresponding nonparametric alternative Mantel-Haenszel or χ^2 test for categorical variables. Using variables that were statistically significant ($p<0.05$, $p<0.1$) at the between-group comparison level, the bivariate logistic regression model was employed to determine the baseline factor odds ratio of failure in exenatide therapy. The significance was considered at the level of $p<0.05$.

Results

Patient disposition, baseline demographic and clinical characteristics

Ninety-three patients received exenatide therapy during the observed period; two were excluded from the study because they stopped therapy for other reasons than poorly regulated blood glucose levels: one because of persistent gastrointestinal adverse events and another one arbitrarily. Out of 91 analyzed patients, 46 (50.5%) were male and 45 (49.5%) female, median age 58 (31-76) years, BMI 38.95±4.35 kg/m^2, duration of diabetes 10 (1-30) years and HbA1c level 8.3±1.4%. Thirty (33%) patients stopped therapy because of glycemic dysregulation during 105 (21-390) days on therapy.

Differences between the groups of drug responders and drug nonresponders by univariate analysis

The following seven variables differed statistically significantly between the two groups of patients, i.e. drug responders (n=61), who achieved and maintained blood glucose control, and drug nonresponders (n=30): fasting blood glucose concentration (p=0.032), serum creatinine concentration (p=0.031), incidence of retinopathy (p=0.009), CKD (p<0.001), CAD (p=0.042), peripheral artery

Table 2. Laboratory findings

	Disease control achieved	Disease control lost	p value, CI 95%
HbA1c (%)	N=60 8.15 (5.5-11.3)	N=25 8.65 (5.5-11.0)	0.418
Fasting serum glucose (mmol/L)	N=60 10.2 (5-19)	N=28 11.5 (5.6-20)	0.032
Postprandial serum glucose (mmol/L)	N=53 12 (4.6-26)	N=25 12.00 (7.0-25.0)	0.899
Fasting C peptide (nmol/L)	N=29 0.82 (0.28-1.84)	N=19 0.53 (0.02-1.97)	0.267
120“ C peptide (nmol/L)	N=16 1.31 (0.34-2.28)	N=15 0.93 (0.02-2.42)	0.353
Insulin resistance-HOMA	N=25 5.2 (1.4-16.10)	N=8 5.05 (1.90-9.70)	0.653
CRP (mg/L)	N=42 4.0 (0.7-75)	N=25 4.4 (0.5-53.60)	0.769
Ferritin (μg/L)	N=40 158.5 (13.860)	N=25 100 (36-491)	0.179
LDL-cholesterol (mmol/L)	N=61 2.85 (1.03-5.8)	N=28 2.98 (1.29-4.38)	0.475
HDL-cholesterol (mmol/L)	N=61 1.24 (0.7-2.1)	N=28 1.24 (0.8-2.5)	0.045
Triglycerides (mmol/L)	N=60 2.0 (0.86-10.89)	N=28 2.2 (0.92-7.27)	0.742
AST (units/L)	N=59 25 (14-53)	N=28 21 (13-56)	0.654
ALT (units/L)	N=57 36 (15-89)	N=28 24.5 (8-68)	0.100
GGT (units/L)	N=58 39.5 (19-118)	N=27 28 (14-149)	0.538
AP (units/L)	N=58 85 (30-131)	N=27 85 (39-126)	0.809
TSH (nmol/L)	N=47 1.64 (0.10-14.07)	N=25 2.26 (0.64-4.79)	0.509
Serum creatinine (μg/L)	N=33 72 (44-124)	N=11 93 (44-149)	0.031
Creatinine clearance (mg/mL/min)	N=40 147 (50-247)	N=26 103 (18-238)	0.590
Albuminuria (mg/24 h)	N=35 11 (3-4056)	N=24 57 (3-1763)	0.914

HOMA = homeostatic model assessment; CRP = C-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase; AP = alkaline phosphatase; TSH = thyroid-stimulating hormone

Table 3. Complications

	Disease control achieved	Disease control lost	p value, CI 95%
Peripheral neuropathy	N=60 Yes 59 (98.4%) No 1 (1.6%)	N=30 Yes 30 (100%) No 0	0.605
Retinopathy	N=61 Yes 17 (27.9%) No 44 (72.1%)	N=30 Yes 17 (56.7%) No 13 (43.3)	0.009
Chronic kidney disease	N=61 Yes 15 (24.7%) No 46 (75.4%)	N=30 Yes 13 (43.3%) No 17 (56.7%)	<0.001
Coronary artery disease	N=61 Yes 19 (31.1%) No 42 (68.8%)	N=30 Yes 16 (53.3%) No 14 (46.7%)	0.043
Peripheral artery disease	N=61 Yes 21 (34.4%) No 40 (65.6%)	N=30 Yes 18 (60%) No 11 (36.7%) Data not available 1 (3.3%)	0.017
Cerebrovascular disease	N=61 Yes 3 (4.9%) No 58 (95.1%)	N=30 Yes 3 (10%) No 27 (90%)	0.368

disease (p=0.017) and concomitant therapy with metformin and exenatide (p=0.04) (Tables 1-4). The group of nonresponders had a higher fasting glucose blood concentration (11.5 mmol/L (5.6-20) *vs.* 10.2 mmol/L (5-19)) and higher serum creatinine concentration (93 μmol/L (44-149) *vs.* 72 μmol/L (44-124)). Nonresponders more frequently showed diabetic complications including retinopathy (56.7% *vs.* 27.9%), CKD (43.7% *vs.* 24.7%), CAD (53.3% *vs.* 31.1%) and peripheral artery disease (60% *vs.* 34.4%). The group of patients who achieved and maintained blood glucose level control on exenatide therapy more often had concomitant metformin and exenatide therapy (82% *vs.* 62%).

Logistic regression

Defining the covariates by variables shown statistically significant (p<0.1) by univariate analysis and therapy outcome as a dependent variable, we applied bivariate logistic regression. The significant risk was found for the following variables: peripheral artery disease, CAD, retinopathy and CKD. Peripheral artery disease increased the risk of exenatide therapy failure by 42.2%, CAD by 39.6%, retinopathy by 29.5% and CKD by 4.7% (Table 5).

Discussion

Since twice daily subcutaneous injection of exenatide has a power of lowering HbA1c by about 0.5%-1%, the ADA/EASD consensus on treatment options for T2DM patients finds it appropriate therapy for patients with glycemic control above target levels as well as monotherapy or in combination with sulfonylurea, metformin and/or thiazolidinediones[16]. In fact, several clinical trials have proven its efficacy in achieving glucoregulation in type 2 diabetic patients. Heine *et al.* as well as Pawaskar *et al.* found it equally or more effective as insulin glargine injection in achieving and sustaining glycemic control in patients with poorly regulated diabetes[17,18]. A pilot study performed by Davis *et al.* suggests that it was feasible to

Table 4. Medication

	Disease control achieved	Disease control lost	p value, CI 95%
Background therapy	N=61 Yes 59 (96.7%) No 2 (3.3%)	N=30 Yes 30 (100%) No 0	0.316
Metformin	N=61 Yes 46 (75.4%) No 15 (24.6%)	N=30 Yes 20 (66.7%) No 10 (33.3%)	0.381
Sulfonylurea	N=61 Yes 26 (42.6%) No 35 (57.4%)	N=30 Yes 9 (30%) No 21 (70%)	0.247
Metformin with exenatide	N=61 Yes 50 (82%) No 10 (16.4%) Data not available 1 (1.6%)	N=30 Yes 18 (60%) No 12 (30%)	0.04
Sulfonylurea with exenatide	N=61 Yes 22 (36.1%) No 35 (57.4%) Data not available 4 (6.6%)	N=30 Yes 16 (53.3%) No 14 (46.7%)	0.147
Antihypertensive therapy	N=61 Yes 56 (91.8%) No 5 (8.2%)	N=30 Yes 28 (93.3%) No 2 (6.7%)	0.797
RAAS	N=61 Yes 56 (91.8%9 No 5 (8.2%)	N=30 Yes 28 (93.3%) No 2 (6.7%)	0.395
HMG-CoA reductase inhibitors	N=61 Yes 50 (82%) No 11 (18%)	N=30 Yes 21 (70%) No 9 (30%)	0.195
Fibric acid derivatives	N=60 Yes 12 (19.7%) No 48 (78.7%)	N=30 Yes 5 (16.7%) No 25(83.3%)	0.725
Antiaggregation agents	N=61 Yes 29 (47.5%) No 32 (52.5%)	N=30 Yes 17 (56.7%) No 13 (43.3%)	0.414

RAAS = renin angiotensin aldosterone system inhibitors; HMG-CoA reductase inhibitors = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

sustain glycemic control when substituting insulin with exenatide[19]. Yet, it is important to note that in all clinical trials with exenatide, a certain number of patients failed to achieve or maintain target blood glucose levels[12-14]. Although a consistent body of literature suggest that GLP-1 secretion is impaired in T2DM patients, recent studies have shown that differences in postprandial GLP-1 levels between T2DM patients and healthy individuals are not as apparent, i.e. the decrement in GLP-1 levels is not a general characteristic of T2DM patients, and that there are many individual factors significantly related to GLP-1 secretory response[20]. Thus, therapy with incretin-based glucose lowering medications including exenatide may not be suitable for all T2DM patients.

In this study, we compared clinical and laboratory parameters between exenatide therapy responders and nonresponders in order to identify the factors that might possibly predict treatment failure. Our findings suggested that patients who did not respond to exenatide therapy showed a higher prevalence of retinopathy, CKD, CAD and peripheral artery disease, i.e. microvascular and macrovascular complications, compared to the cohort of exenatide responders. As persistent hyperglycemia and hyperinsulinemia lead to development of microvascular and macrovascular complications, we find it reasonable to consider that the presence of microvascular and macrovascular complications in T2DM patients emphasizes longer disease duration or higher blood glucose levels for a longer period of time. Together with not significant but still worse fasting lipid profile in the nonresponder group, it may exert a glucotoxic as well as lipotoxic action and subsequently lead to greater β cell exhaustion. Additionally, although not shown as statistically significant, the group of nonresponders were older and had longer disease duration. They also had slightly higher fasting glucose levels and HbA1c levels, while lower both fasting and 120“ C peptide levels in comparison to the responder group. These findings indicated the presence of lower endogenous basal insulin levels and lower postprandial endogenous insulin levels as well. That might con-

Table 5. Bivariate logistic regression analysis

	OR	P value	95% CI
Peripheral artery disease	0.426	0.05	0.222-0.818
Coronary artery disease	0.396	0.04	0.183-0.856
Retinopathy	0.295	0.009	0.095-0.921
Chronic kidney disease	0.047	<0.001	0.001-0.164
Metformin with exenatide	2.456	0.056	0.669-9.01
Serum creatinine level	1.042	0.015	0.964-1.126
Fasting glucose level	1.076	0.287	1.059-1.092

tribute to the confirmation of exenatide insulinotropic effect as its main glycemic management action pathway. Additionally, Andersen *et al*. also showed the higher baseline HbA1c level to be a good predictor in identification of exenatide responders[21]. However, Buysschaert *et al*. found the exenatide therapy regimen to be effective independently of baseline HbA1c levels, weight, BMI, age and duration of diabetes[22]. Like DeFronzo *et al*., we also found a higher rate of exenatide/metformin dual therapy in the group of responders[12]. We explain it by the fact that metformin enhances insulin sensitivity, and the combination of two different therapeutic pathways usually manage to sustain feasible glycemia control.

Higher diastolic blood pressure and higher serum creatinine levels in our nonresponder group may indicate more severe CKD that may lead to higher activity of the circulating GLP-1 degradation enzyme dipeptidyl peptidase-4 (DPP4), which is already elevated in hyperglycemia state[23,24]. In fact, DPP4 has recently been identified as a novel adipokine that impairs insulin signaling in three different primary cell types: adipocytes, skeletal muscle and smooth muscle cells[25]. This finding potentially links elevated DPP4 levels to the higher rate of insulin resistance, which cannot be overcome by exenatide insulinotropic effect. We did not perform DPP4 plasma levels or DPP4 plasma activity analysis in our study and did not find statistically significant difference in insulin resistance between the two groups of patients. However, it is important to note that we had approximately 1/3 of missing data in each group for this variable, which gives the possibility of irrelevant result. However, DPP4 levels in T2DM patients both with and without vascular complications represent a highly significant area for further study evaluation.

In conclusion, we found it reasonable to consider that a higher rate of microvascular and macrovascular complications in nonresponder group might reflect exhausted reservoirs of endogenous insulin and those complications may be a good predictor of failure of exenatide therapy in the majority of patients. However, whether detection of a higher rate of chronic complications in T2DM has a predictive value for efficacy of GLP-1 based therapy needs to be assessed in further follow-up studies.

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Sažetak

POVEZANOST VASKULARNIH KOMPLIKACIJA S IZOSTANKOM TERAPIJSKOG UČINKA EKSENATIDA U BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 2

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Eksenatid je inkretinski mimetik koji djeluje putem receptora proteina nalik glukagonu 1, široko prihvaćen kao uspješan novi lijek u terapiji šećerne bolesti tipa 2. Svrha ovoga istraživanja bila je istražiti moguće čimbenike predviđanja učinkovitosti terapije analizom osnovnih nalaza među bolesnicima sa šećernom bolešću tipa 2. Provedena je analiza antropometrijskih obilježja, laboratorijskih nalaza i evaluacija dijabetičnih komplikacija kod 91 bolesnika koji su započeli terapiju eksenatidom. Bilo je 46 (50,5%) bolesnika muškog spola i 45 (49,5%) ženskog spola; medjian dobi bio je 58 (31-76) godina, indeks tjelesne mase 38,95±4,35 kg/m^2, trajanje šećerne bolesti 10 (1-30) godina s prosječnom vrijednosti HbA1c 8,3±1,4%. Tridesetoro (33%) bolesnika prekinulo je terapiju zbog loše regulacije glikemije tijekom 105 (21-390) dana. Sedam varijabli statistički ih je razlikovalo od skupine koja je postigla zadovoljavajuću glukoregulaciju na eksenatidu: više vrijednosti glukoze natašte (11,5 mmol/L (5,6-20) prema 10.2 mmol/L (5-19), više vrijednosti kreatinina u serumu (93 μmol/L (44-149) prema 72 μmol/L (44-124), viša učestalost razvijenih dijabetičnih komplikacija: retinopatije (56,7% prema 27,9%), kronične bubrežne bolesti (43,7% prema 24,7%), koronarne arterijske bolesti (53,3% prema 31,1%) i periferne arterijske bolesti (60% prema 34,4%), te rjeđa upotreba metformina u kombinaciji s eksenatidom (62% prema 82%). Bivarijatna logistička regresija identificirala je perifernu arterijsku bolest, koronarnu arterijsku bolest, retinopatiju i kroničnu bubrežnu bolest kao statistički značajne čimbenike rizika za disregulaciju glikemije na terapiji eksenatidom. Navedeni rezultati navode na zaključak kako bi razvijene mikrovaskularne i makrovaskularne komplikacije mogle biti čimbenik koji predviđa neuspjeh glukoregulacije eksenatidom.

Ključne riječi: *Eksenatid, glukagonu sličan peptid 1; Dijabetes melitus, tip 2; Vaskularne komplikacije, dijabetične*