



# Insulin Resistance and Contrainsular Response in Type 2 Diabetes Mellitus Patients with Acute Coronary Syndrome

Dinara N. Sheryazdanova<sup>1\*</sup>, Yelena M. Laryushina<sup>1</sup>, Larissa Ye. Muravlyova<sup>2</sup>, Lyudmila G. Turgunova<sup>1</sup>, Assel R. Alina<sup>1</sup>, Natalya V. Vassilyeva<sup>1</sup>, Anar A. Turmukhambetova<sup>3</sup>

<sup>1</sup>Department of Internal Medicine 2, Karaganda Medical University, Karaganda, Kazakhstan; <sup>2</sup>Department of Biological Chemistry, Karaganda Medical University, Karaganda, Kazakhstan; <sup>3</sup>Department of Strategic Development, Karaganda Medical University, Research and International Collaboration, Karaganda, Kazakhstan

## Abstract

**BACKGROUND:** The number of patients with diabetes mellitus (DM) is progressively increasing all over the world. Over the past three decades, the global burden of diabetes has increased from 30 million in 1985 to 382 million in 2015, and current trends indicate that the prevalence of diabetes grows progressively. The phenomenon of insulin resistance established in the majority of type 2 DM (T2DM) patients. T2DM is associated with  $\beta$ -cell deficiency,  $\alpha$ -cell resistance to insulin, and reduced effects of incretin. However, the role of insulin and glucagon in the process of cardiovascular complications in diabetic patients is a matter of debate.

**AIM:** Our study aims to estimate insulin resistance and the contrainsular response in patients with T2DM and acute coronary syndrome (ACS).

**METHODS:** The 104 T2DM patients aged 18–70 years participated in the observational study carried out in the Karaganda regional cardiosurgery hospital and ambulatory. The first group included 37 patients hospitalized for ACS in the first 24 h of admission. The second group included 67 patients without ACS. Determination of insulin resistance and contrainsular response was provided using a multiplex immunological assay with XMap technology on Bioplex 3D.

**RESULTS:** During the research, we have discovered a decreased level of glucagon and increased homeostasis model assessment of insulin resistance (HOMA-IR) in patients with T2DM diabetes and ACS. Evaluation of traditional correlation interactions of HOMA-IR and indicators of carbohydrate metabolism showed a positive correlation with fasting plasma glucose in both study groups (Group 1:  $R = 0.47$ ,  $p = 0.003$ ; Group 2:  $R = 0.41$ ,  $p = 0.024$ ). Glucagon-like peptide (GLP)-1 has a weak positive correlation with HOMA-IR only in the first group ( $R = 0.32$ ,  $p = 0.006$ ). Increased insulin resistance was associated with high GLP-1 levels and low glucagon. The logistic regression model established that an increased HOMA-IR index rises the chance of ACS by 10.6% ( $OR = 1.106$  [95% CI 1.105–1.206],  $p = 0.021$ ). The logistic regression model, reflecting the relation between glucagon and ACS, shows that increased glucagon reduces the ACS odds ( $OR = 0.989$  [95% CI 0.979–0.999],  $p = 0.026$ ). The adjusted regression model showed no significant influence of early presented factors on the probability of ACS.

**CONCLUSION:** There is a trend toward elevated HOMA-IR insulin resistance index and decreased level of glucagon in diabetic patients with ACS.

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\*Correspondence: Dinara Sheryazdanova, Department of Internal Medicine 2, Karaganda Medical University, Karaganda, Kazakhstan.

E-mail: sheryazdanova.dinara@gmail.com

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Yelena M. Laryushina, Larissa Ye. Muravlyova,

Lyudmila G. Turgunova, Assel R. Alina,

Natalya V. Vassilyeva, Anar A. Turmukhambetova

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## Introduction

About 32.2% of all patients with type 2 diabetes mellitus (T2DM) around the world have cardiovascular diseases. Coronary artery disease and ischemic stroke cause approximately half of all deaths among people with diabetes [1].

The connection between T2DM and cardiovascular disease is undiscussable. Diabetes is considered one of the major independent cardiovascular risk factors, independent of additional confounders such as age, arterial hypertension, smoking, hypercholesterolemia, and left ventricular hypertrophy [2]. The mortality rate in patients with T2DM from macrovascular complications allows the researchers to think about its decisive importance for the further prognosis of the disease [3].

The fundamental pathogenetic role of hyperinsulinism in T2DM is established in many longitudinal studies [4], [5]. Insulin resistance criteria homeostasis model assessment of insulin resistance (HOMA-IR) associated with high cardiovascular risk have been shown in several studies [6], [8]. Increased insulin concentration elevates the risk of adverse cardiovascular outcomes in adult patients after coronary revascularization [9], [10]. However, the diagnostic significance of the quantitative assay of insulin resistance was insufficiently studied in T2DM and adverse cardiovascular events.

The simplest criteria of insulin resistance are HOMA-IR [11], [12], [13]. The association of HOMA-IR with a high cardiovascular risk is established in some studies of patients without diabetes [14], [15]. Nevertheless, the crosslink of HOMA-IR with the level of cardiovascular risk among patients with established type

2 diabetes is controversial. In the Verona Diabetes Study, the Veteran's Affairs Diabetes Trial, and the study of high-density lipoprotein (HDL) in patients with percutaneous coronary intervention, HOMA-IR is associated with an increased risk of cardiovascular events [16], [17]. The opposite trend with no link between HOMA-IR and adverse cardiovascular events is described in a study of cardiovascular risks in the UK [18].

At the same time, biomarkers of the contransular response are considered valuable pathogenetic biomarkers of T2DM. One of the important agents of this group is glucagon. In addition to the contransular action, glucagon plays a significant role in maintaining heart and kidneys function. Moreover, in the medical practice of the previous years, glucagon has been therapeutically used to treat heart failure.

In physiological conditions, glucagon secretion is regulated by insulin and somatostatin, as the main paracrine/endocrine inhibitors. Many other agents such as glucose, incretins (glucagon-like peptide (GLP)-1, amylin, leptin, fatty acids, ketone bodies, glucose-dependent insulinotropic peptide (GIP), amino acids as L-arginine, and leucine could regulate its secretion. Meyer *et al.* demonstrated that GLP-2 can also stimulate glucagon secretion [19], [20].

Pathogenetic molecular changes in T2DM could be schematically characterized by  $\beta$ -cell deficiency,  $\alpha$ -cell resistance to insulin, and reduced effects of incretins. B-cell deficiency develops gradually, due to partial loss of their mass and dysfunction under the influence of genetic background of glucotoxicity and lipotoxicity and the advanced products of enhanced glycation [21]. Presumably, hyperglycemia induces long-term, self-sustaining processes in the vessels which are associated with oxidative stress and chronic inflammation. They play an important role in the "metabolic memory" phenomenon and insulin resistance process, as well as in the diabetic macro and microvascular complications development [22], [23].

The aim of the study was to evaluate the indicators of insulin resistance including insulin and C-peptide, and contransular response including glucagon and GLP 1, GIP in patients with type 2 diabetes and cardiovascular events (acute coronary syndrome [ACS]).

## Materials and Methods

### Study subjects

We conducted an observational cohort study of 104 patients with type 2 diabetes, aged 18–70 years old. The inclusion criteria were preexisting T2DM, either with the ACS at the first 24 h from the initial symptoms of a cardiovascular event or diabetic patients with cardiovascular

risk factors: Arterial hypertension, abdominal obesity, and dyslipidemia without cardiovascular events in medical history. Exclusion criteria were pregnancy, severe mental, and oncological diseases.

The sample size was calculated by the Kelsey method using EPI info software for unmatched cohort studies with a two-sided confidence level of 95%, power is 80%, the ratio of unexposed to exposed cases is 2. The presence of outcomes (ACS in diabetic patients) was taken from the previous studies. The minimum exposed cases are 35 and unexposed is 69. The time of data collection was from October 2017 to June 2018 at Karaganda regional cardiosurgery hospital and different ambulatories of Karaganda city, Kazakhstan.

### Data collection

The study inclusion process was started with the procedure of gaining signed informed consent. In both study groups, medical history, clinical examination, anthropometry, arterial blood pressure, plasma glucose, lipid profile, and glycosylated hemoglobin (HbA1c) were collected. Physical examination included blood pressure measurement according to principles of the World Health Organization using a mechanical tonometer (Microlife BP AG1-10) on both hands with at least 10 min rest preliminary period [24]. The lowest of three consecutive measurements were taken for future calculations. Bodyweight and height were measured using a digital stadiometer with scales (TBEC RS-232). The body mass index (BMI) was calculated as body weight divided on a square of height in meters ( $\text{kg}/\text{m}^2$ ). Waist circumference (WC) was measured with non-elastic measuring tape on the thinnest part of the corpus.

### Blood samples

Blood glucose measurement was provided using a glucose meter (Accu-Chek Active). The diagnosis of T2DM was established on the HbA1c level greater or equal 6.5% by the 1997 American Diabetes Association [25]. HbA1c concentration was established with the NycoCard test system from venous blood by reflectometry method using the NycoCard Reader II blood analyzer. All the parameters of lipid profile (total cholesterol [TC], low-density lipoprotein cholesterol [LDL cholesterol], HDL cholesterol [HDL cholesterol], and triglycerides [TGs]) were estimated in plasma by the method of selective precipitation with phosphotungstate and magnesium.

Plasma samples were stored at  $-70^\circ\text{C}$  for not more than 3 months. We used method of the magnetic bead-based multiplex immunoassay using XMap technology for detecting insulin, C-peptide, glucagon, GLP-1, and GIP. The standard Bio-Plex Pro Human Diabetes, 10-Plex Panel kit was used to determine the concentration of listed metabolites in accordance with "Overnight protocol" by the instruction of the manufacturer. The protocol consisted of three steps. The first step was

the incubation of unknown, standard, and control samples with magnetic beads loaded with primary antibodies. The second step was the revelation using detecting antibodies and Streptavidin Phycoerythrin Conjugated. The third step of the protocol was fluorescence registration using Bioplex 3D equipment (Luminex software). All detected analytes with minimum detectable concentration have a coefficient of variation <10%.

### Statistical analysis

We conducted the Kolmogorov–Smirnov test for verification of the normal distribution of data. The description of the quantitative data was carried out by the median and quartiles. The Mann–Whitney U-test or t was used to compare two independent parameters. The association of insulin resistance and contrainsular response was evaluated using the Spearman correlation coefficient and the binary logistic regression model. We use age, gender, treatment, social, and demographic characteristics for adjusted risk calculation. Statistical analysis was provided on IBM SPSS Statistics software, ver. 22.0. Results were considered statistically significant at  $p < 0.05$ .

## Results

The participants' baseline characteristics are presented in Table 1. The first group included 37 patients with T2DM and ACS, the second group comprised 67 T2DM patients without ACS. In the first group, there is bias to male patients. The median age of patients in the first group was higher than the second. Significant differences are also found among patients by the educational level and marital status. The number of participants with graduate education is lower in the ACS group in comparison with participants without ACS. Comparison of marital status same as the duration of T2DM shows the almost equal percentage of participants in both groups.

**Table 1: Baseline characteristics participants (n = 104)**

Parameter	1 <sup>st</sup> group (T2DM with ACS), n = 37	2 <sup>nd</sup> group (T2DM without ACS) n = 67	p
Age, years	59.00 (54.00, 63.25)	49.50 (37.50, 56.75)	0.001
Male (42)	24 (64.8)	16 (23.9)	0.012
Female (62)	13 (35.2)	51 (76.1)	0.017
Middle school course	23 (62.2)	39 (58.2)	0.112
Graduate education	14 (37.8)	28 (41.8)	0.019
Single	14 (37.8)	15 (22.4)	0.889
Married	23 (62.2)	52 (77.6)	0.013
Duration of T2DM, years	5.00 (2.00, 15.25)	6.00 (3.00, 12.50)	0.960

Categorical variables are present as n (%); non-parametric distributed continuous variables as median (first quartile, third quartile). Mann–Whitney U-test was used for non-parametric continuous variables,  $\chi^2$  test was used for categorical variables

Clinical and laboratory findings are presented in Table 2. In the group of patients with T2DM and ACS, compared with the group without ACS, there is a significant increase of traditional cardiovascular risk factors such as systolic blood pressure, diastolic blood pressure, and increased LDL level.

**Table 2: Clinical and laboratory findings**

BMI, kg/m <sup>2</sup>	30.76 (25.10, 34.37)	28.43 (25.08, 32.65)	0.193
WC, cm	96.00 (92.00, 103.00)	91.00 (80.00, 107.25)	0.286
SBP, mm of mercury	130.00 (120.00, 150.00)	120.00 (110.00, 130.00)	0.027
DBP, mm of mercury	80.00 (80.00, 90.00)	80.00 (70.00, 80.00)	0.008
LDL, mmol/l	0.92 (0.75, 1.19)	1.10 (0.87, 1.33)	0.041
HDL, mmol/l	4.51 (3.20, 5.27)	3.96 (3.12, 4.40)	0.176
TG, mmol/l	1.39 (0.77, 1.73)	1.22 (0.68, 1.85)	0.550
C-peptide, ng/ml	1430.03 (831.63, 2641.85)	1098.35 (754.22, 2436.73)	0.715
GLP-1, ng/ml	113.47 (70.42, 141.91)	82.95 (54.70, 134.75)	0.185
GIP, ng/ml	252.26 (130.92, 670.85)	233.50 (126.84, 398.20)	0.226
Glucagon, ng/ml	57.79 (51.11, 150.26)	1377.77 (418.10, 6078.86)	<0.001
Insulin, mU/L	14.96 (5.87, 26.27)	7.29 (4.20, 20.59)	0.077
HOMA-IR	4.58 (1.62, 9.55)	1.95 (0.876, 6.56)	0.035
T2DM treatment			
Metformin	23 (62.2)	43 (64.2)	0.786
Sulfonylurea	9 (24.3)	13 (19.4)	0.634
IDPP4	1 (2.9)	4 (5.9)	0.606
Insulin	4 (10.8)	7 (11.9)	0.064

GIP: Gastric inhibitory polypeptide, BMI: Body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Estimation of insulin resistance provided by HOMA-IR calculation revealed an increased level of this parameter in patients with T2DM and ACS. A similar trend was noted for glucagon levels. There are no differences found by the middle school course, BMI, WC, plasma glucose level, HbA1c, TC, LDL cholesterol, TG, C peptide, GIP, and insulin.

Patients received one of three oral hypoglycemic agents: Metformin, sulfonylurea, DPP4 inhibitors (dipeptidyl peptidase-4 inhibitors), or insulin. No significant differences were found in the number of patients by prescribed therapy.

Assessment of correlation (Table 3) between the level of insulin resistance and anthropometric indicators revealed a middle positive correlation between HOMA-IR and BMI ( $R = 0.65$ ,  $p = < 0.001$ ). Similar upward trend revealed for the patients from the second group ( $R = 0.47$ ,  $p = 0.010$ ). A significant positive correlation of HOMA-IR with WC was noted only for a group of patients with T2DM and ACS. In both studied groups, there is a significant correlation between HOMA-IR and weight. Stronger interaction was in patients with T2DM without ACS (first group:  $R = 0.32$ ,  $p = 0.006$ ; second group:  $R = 0.62$ ,  $p \leq 0.001$ ). An assessment of traditional correlation interactions of HOMA-IR and carbohydrate indicators showed an average positive correlation with fasting plasma glucose in both groups studied (the first group:  $R = 0.47$ ,  $p = 0.003$ ; the second group:  $R = 0.41$ ,  $p = 0.024$ ). GLP-1 responsible for the contrainsular response has a weak positive correlation with HOMA-IR only in the group of patients with T2DM and ACS ( $R = 0.32$ ,  $p = 0.006$ ). Increased insulin resistance is associated with an increased GLP-1 level and a decreased glucagon level.

**Table 3: Correlation coefficients of HOMA-IR**

Parameter	1 <sup>st</sup> group (T2DM with ACS)		2 <sup>nd</sup> group (T2DM without ACS)	
	R	P	R	P
BMI	0.65	<0.001	0.47	0.010
Plasma glucose	0.47	0.003	0.41	0.024
WC	-0.18	0.474	0.49	0.002
Weight	0.32	0.036	0.62	0.001
HbA1c	0.16	0.409	-0.08	0.661
C-peptide	0.01	0.964	0.06	0.716
GLP-1	0.294	0.007	0.13	0.506
Glucagon	-0.09	0.653	0.11	0.506

WC: Waist circumference



A binary logistic regression model that assesses the effect of insulin resistance (Table 4) revealed that an increased HOMA-IR index significantly enhances the chance of ACS by 10.6%, OR = 1.106 (95% CI 1.105–1.206).

**Table 4: Model of binary logistic regression for HOMA-IR, glucagon, and adjusted regression model for HOMA-IR and glucagon**

Parameter	Significance	Odds ratio	95%CI for exp (B)	
			Lower	Upper
Model 1				
HOMA-IR	0.021	1.106	1.015	1.206
Model 2				
Glucagon	0.026	0.989	0.979	0.999
Model 3 Model of binary logistic regression for HOMA-IR and glucagon adjusted for age, gender, marital status, and treatment				
Glucagon	0.539	1.000	1.000	1.001
Insulin	0.614	0.999	0.997	1.002
HOMA-IR	0.660	1.040	0.874	1.238

The binary logistic regression model, representing the relationship of the glucagon level with the ACS odds, shows that increased glucagon concentration significantly reduces the chance of the ACS onset (OR = 0.989 [95% CI 0.979–0.999]).

The model of binary logistic regression adjusted for age, gender, education, marital status, and treatment does not reveal any significant impact of HOMA-IR and glucagon on the probability of ACS. However, such cofounders as male gender (OR = 52,779 [95% CI 4.687–94.391]) and age (OR = 1.193 [95% CI 1.036–1.375]) increase the ACS odds. The graduate education (OR = 0.012 [95% CI 0.000–0.324]) reduces the probability of ACS.

## Discussion

We have obtained the unambiguous data reflect the negative effect of insulin resistance on cardiovascular safety in our study. The level of HOMA-IR in patients with DM was higher during the ACS period than in similar patients with diabetes without ACS. It is also associated with an increased chance of an adverse cardiovascular event. At the same time, an increased level of HOMA-IR and decreased level of glucagon established an impact on the odds ratio of ACS [26]. The obtained results can be explained by the studies of  $\alpha$ -cells insulin resistance in T2DM.  $\alpha$ -cells can be resistant to the inhibitory action of insulin or other  $\beta$ -cell secretory products, such as zinc or  $\gamma$ -aminobutyric acid [27].

In our research, glucagon shows diagnostic value in ACS prognosis. Moreover, glucagon shows greater significance than HOMA-IR in constructing a combined prognostic model of logistic regression. The impact of glucagon can be explained by the modern conception of DM pathogenesis. Diabetes is characterized by fasting hyperglycemia and impaired glucose-induced suppression of glucagon in the postprandial state. This condition arises mainly due to  $\beta$ -cells apoptosis and bias

of the  $\beta/\alpha$ -cells ratio to  $\alpha$ -cells. The condition contributes to decreased insulin to glucagon ratio. Furthermore,  $\beta$ -cells can dedifferentiate to pluripotent predecessor cells that can release glucagon and somatostatin, thereby further reducing the insulin/glucagon ratio [28]. In this context, it seems clear that glucagon, with a certain reserve of its secretion, plays a major role in the reduction of metabolic effects of exceeding insulin secretion [29]. Besides, T2DM is characterized by a reduced effect of incretins, which progresses with the duration of the disease. Although the effects of GLP-1 are relatively preserved, prolonged hyperglycemia is capable of gradually suppressing the contrainsular response, creating a vicious cycle [30], [31].

The results obtained in our study did not match the concept that higher glucose level leads to the increased probability of ACS. According to such iconic studies as UKPDS and VADT, the glucose reduction is associated with a lower number of cardiovascular events and mortality in type 2 diabetes [32], [33], [34]. The data from these studies suggest that the glucose-lowering conception that predominates in modern diabetology required achieving the target HbA1c level to reduce the risk of diabetic complications.

The number of patients who reached the target level of HbA1c in the groups with type 2 diabetes and ACS and T2DM without ACS was not statistically different. Besides, patients with and without ACS did not have statistical differences in HbA1c level. The data of our study can be supported by the results of such large projects as the prospective observational study of the Verona Diabetes Study, where the main independent predictor of death in patients with diabetes was not HbA1c level, but glycemic variability [35].

The TC level, despite the increased level in both study groups, is not associated with ACS in our study. This fact corresponds to the results of many other studies that do not show the effectiveness of TC reduction to prevent the myocardial infarction risk [36].

In our study, there were no significant differences in LDL levels found between study groups. This fact contradicts the widely accepted theory of atherogenesis. These results can be explained by the limitation of the study as a small sample. One explanation is that our study has a small sample size; therefore, it is limited in a score. Unlike hypercholesterolemia, the manifestation of dyslipidemia in the form of a decreased serum HDL is identified as a more significant factor associated with the onset of an ACS, which is also established in our study [37], [38]. The average HDL concentration in the T2DM patients without ACS corresponds to the recommended target value, while in the T2DM patients with ACS, the average HDL level is below the recommended level.

## Limitations

This study has potential limitations. The effects estimated in these models are based on a cohort study

with relatively small sample size. The sample, selected for this study, was specifically patients with well-controlled T2DM, thus the results may not be applicable for diabetic patients outside of this designation. Future prospective studies suggested to estimate insulin and glucagon secretion in a more detailed way.

## Conclusion

The results of our study showed that there is a trend toward elevated HOMA-IR and decreased level of glucagon in diabetic patients with ACS. However, this trend does not show significant impact on the ACS development probability. HOMA-IR and glucagon are possibly present a potential role in cardiovascular events in patients with T2DM.

## Authors' Contributions

Sh.D, Ye.L., L.M., and A.A. carried out the experiment and wrote the manuscript with support from L.T. and N.V. A.T. helped supervise the project. D.Sh., Ye.L., and A.T conceived the original idea. All authors discussed the results and contributed to the final manuscript.

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