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Association between 1,5-anhydro-D-sorbitol, Insulin, and Incretins in Patients with Pre-diabetes and ST-elevation Myocardial Infarction

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Abstract

BACKGROUND: Pre-diabetes itself could be an independent predictor of such adverse cardiovascular events as myocardial infarction and ischemic stroke. Since pre-diabetes is linked with hyperinsulinism, it could also cause fluctuations of incretins concentration. Another significant fact related to pre-diabetes is glycemic variability. The impact of these factors on pre-diabetes and acute myocardial infarction is a promising phenomenon to the study.

AIM: The study aims to estimate insulin, incretins, and glycemic variability in patients with impaired carbohydrate metabolism and acute myocardial infarction.

METHODS: The 255 pre-diabetes patients participated in the observational case–control study. The first group included 85 patients hospitalized for ST-segment elevation myocardial infarction (STEMI). The second group included 170 patients without STEMI. Insulin and incretins were measured using a multiplex immunological assay with XMap technology on Bioplex 3D. The high-performance liquid chromatography with mass spectrometry was used to evaluate 1,5-AG concentration. The binary logistic regression was performed to evaluate the association between studying parameters and STEMI.

RESULTS: The insulin secretion parameters showed higher insulin and C-peptide level in patients with STEMI. A similar trend was noted for the HOMA-IR index. Among incretin, we revealed a higher level of glucagon and reduced glucagon-like peptide-1 (GLP-1) in patients with STEMI. The level of 1,5-AG in STEMI patients was significantly lower than in non-STEMI patients. The logistic regression model shows that a lower plasma concentration of 1,5-AG increases the odds of STEMI in patients with pre-diabetes [OR 2.304 (95% confidence interval [CI] 1.980–2.973), p = 0.018]. Reduced GLP-1 concentration also increased the odds of STEMI [OR 1.775 (95% CI 1.460–1.990), p = 0.001].

CONCLUSION: We discovered the association between 1,5-AG, GLP-1, and STEMI in patients with pre-diabetes. It is designating their potential role as cardiovascular risk markers in non-diabetic patients with impaired glucose metabolism.

Introduction

The World Human Organization reports that diabetes mellitus (DM) is a serious reason for morbidity and mortality [1]. The treatment of diabetic patients is a significant burden for the budgets of the national health-care system. Every country annually spends not <5% on the treatment of diabetes [2]. Usually, long-lasting pre-diabetes precedes the onset of diabetes. Moreover, pre-diabetes is a pathological condition that is considered an independent predictor for adverse cardiovascular outcomes [3].

Increased insulin concentration is considered the main pathogenetic chain of diabetes. Excess insulin production occurs much earlier than the hyperglycemic syndrome; however, only hyperglycemia is used to establish diabetes in clinical practice [4]. Researchers evaluate hyperinsulinism and subsequent insulin resistance like independent risk factors of the endothelial lesion [5]. In turn, endothelial dysfunction could lead to cardiovascular complications through the phenomenon of glycemic variability.

Glycemic variability is a physiological phenomenon. Glucose concentrations of healthy people are in the range of 3.3–7.8 mmol/l. The outrange values are rare. The amplitude of glycemic values in patients with DM significantly increases [6]. Glycemic variability is measured routinely by continuous glucose monitoring; however, it also can be evaluated by 1,5-anhydro-D-sorbitol (1,5-AG) concentration in plasma [7].

Some researchers associate pathogenetic mechanisms of glycemic variability with fluctuations of insulin levels in diabetic patients [8]. The mechanism of glycemic variability seems to be a more complex process. Glycemic variability is influenced not only by insulin but also by incretin hormones, which demonstrate a potential cardioprotective effect in

patients with Type 2 diabetes mellitus (T2DM). The studies show the beneficial effects of glucagon-like peptide-1 (GLP-1) receptor agonists on mortality from cardiovascular disease and renal outcomes in patients with T2DM [9].

Since the rise of cardiovascular events has been recorded not only in T2DM but also in patients with pre-diabetes, we considered it promising to study the glycemic variability, insulin resistance, and incretin response in patients with impaired carbohydrate metabolism and acute myocardial infarction who was not previously diagnosed with DM Type 2 [10].

Table 1: Anthropometric and sociodemographic characteristics of participants (n = 255)

Parameter	Group 1 "STEMI+" Median (Q25–75) n = 85	Group 2 "STEMI-" Median (Q25–75) n = 170	p-value
Age, years	51 (46–57)	49 (42–55)	0.071
BMI, kg/m^2	28.7 (24.5–32.2)	27.2 (23.8–30.9)	0.083
WC men, cm	98.0 (89.05–106.5)	99.0 (88.0–105.0)	0.056
WC women, cm	96.5 (93.5–101.3)	88 (75.0–100.0)	<0.001
Systolic blood pressure, mm. Hg	130.0 (120.0–140.0)	120.0 (110.0–140.0)	0.062
Diastolic blood pressure, mm. Hg	80 (80–90)	80 (70–90)	0.074
Fasting blood glucose, mmol/l	5.8 (5.1–6.6)	5.5 (5.2–5.8)	<0.001
HbA1c, %	6.3 (5.3–6.5)	5.7 (5.4–5.9)	0.048
TC, mmol/l	5.6 (4.3–7.7)	5.5 (4.6–6.8)	0.777
HDL-C, mmol/l	0.9 (0.8–1.1)	1.1 (0.8–1.4)	0.069
LDL-C, mmol/l	3.9 (3.1–4.4)	3.8 (3.2–5.1)	<0.001
TG, mmol/l	1.5 (1.1–2.2)	1.1 (0.7–1.6)	<0.001

Methods

We conducted an observational case–control study. The sample size for "cases" and controls was calculated by the Kelsey method for unmatched case–control studies using EPI info statistical software. The minimum number of patients was 53 in the "case" group, and 106 in the "control" group. The two-sided confidence level is 95%, the power is 80%, and the ratio of exposed to non-exposed cases is 2.

Our study included 255 participants. The "case" group (further Group 1) had 85 patients with pre-diabetes and ST-segment elevation myocardial infarction (STEMI). The STEMI duration was no longer than 24 h before admission. Blood samples were taken at admission to the hospital. The questioning was provided on the 3 day of hospitalization. The "control" group (further Group 2) had 170 pre-diabetes patients without STEMI. The eligibility criteria for Group 2 were cardiovascular risk factors such as arterial hypertension, dyslipidemia, and abdominal obesity. The participants from this group were randomly selected from the outpatients' clinic and further invited for questioning and blood samples collection. The blood samples were taken the next day after questioning after 12 h fasting period.

The recruitment period was from April to November 2018 in the Karaganda Cardiac Surgery Center and outpatient department #1 of Karaganda city. The age of the patient was over 18 years. The exclusion criteria were pregnancy, psychiatric disorders, and malignancies. The recruited patients received complete information about the study and signed informed consent. The study protocol was approved by the Local Institutional Review Board with permission number No 309 from May 19, 2017.

The arterial blood pressure was measured on both hands using a mechanical tonometer (Microlife BP AG1-10). According to the recommendation, the blood pressure was measured 3 times after at least 10 min of rest. The lowest numbers were taken. The criteria of the European Society of Hypertension and the European Society of Cardiology were used to provide the classification of arterial blood pressure [11].

The digital stadiometer and scales (TBEC RS-232) were used to measure the weight and height of studied people. The body mass index (BMI) was calculated using the formula BMI = kg/m^2, where the patient's weight was in kilograms and height was in meters square. We established an overweight state at BMI 25–29.9 kg/m^2 and obesity at BMI ≥ 30 kg/m^2. The obesity classification consisted of I grade (BMI 30.0–34.9 kg/m^2), II grade (BMI 35.0–39.9 kg/m^2), and III grade (BMI ≥ 40 kg/m^2).

Table 2: Insulin, incretin response, and 1.5-AG

Parameter	Group 1 "STEMI+" Median (Q25-75) n = 85	Group 2 "STEMI-" Median (Q25–75) n = 170	p-value
C-peptide, ng/ml	1024.2 (733.3–1442.6)	1221.5 (868.5–1846.4)	0.008
Insulin, μIU/ml	11.2 (5.9–26.3)	6.9 (4.3–11.8)	<0.001
HOMA-IR	2.8 (1.3–7.39)	1.6 (0.9–2.7)	0.014
Glucagon, ng/ml	251.7 (80.5–279.83)	191.57 (56.7–1305.7)	0.003
GLP-1, ng/ml	63.1 (42.4–114.6)	80.6 (46.1–98.7)	<0.001
Ghrelin, ng/ml	485.1 (319.5–810.4)	460.7 (290.8–653.9)	0.134
GIP, ng/ml	144.8 (80.5–279.8)	170.1 (114.6–323.5)	0.059
1,5-AG, μmol/l	301.5 (231.6–393.9)	314.6 (250.8–415.1)	0.001

The non-elastic tape was used to measure waist circumference (WC). The point of measurement was in the middle of the low edge of the last palpable rib and upper part of the iliac crest. The criteria for abdominal obesity were at WC> 94 cm in men and WC> 80 cm in women.

The glucose meter (Accu Chek active) was used to determine capillary glucose level. We used pre-diabetes criteria provided by the American diabetes association, then the HbA1c level was more or equal to 5.7% but lower than 6.5% [12]. The STEMI was established by electrocardiographic criteria and a positive troponin test [13].

The parameters of carbohydrate metabolism were estimated using different laboratory methods. The fasting plasma glucose and HbA1c were measured in capillary blood. We used an Accu chek active glucose meter and the Nyco-Card reflectometer. The lipid profile included total cholesterol, low-density lipoproteins cholesterol, high-density lipoproteins cholesterol, and triglycerides. Their concentration was detected in venous blood by the biochemical method of selective precipitation with phosphovolphramate and magnesium

on VitaLine automatic analyzer. The insulin, c-peptide, glucagon, GLP-1, ghrelin, and gastric inhibitory polypeptide (GIP) were measured by XMap Bio-Plex 3D multiplex immunoassay. The high-performance liquid chromatography with mass spectrometry was used to evaluate 1,5-AG concentration.

Statistical analysis

The normal distribution check was done using the Kolmogorov–Smirnov test and Shapiro–Wilk test. The distribution was considered normal at p level < 0.05. We used the χ^2 test for categorical variables and Mann–Whitney U-test for non-parametric continuous variables to compare the corresponding parameters in groups. The binary logistic regression was used to find the association of 1,5-AG, insulin resistance, and incretins (explanatory variables) with STEMI (response variable). The explanatory variables had two categories: "Normal" and "increased." The variable considered increased if its concentration was higher than two standard deviations below the control group's mean. The response variable had two categories: "0" - STEMI, "1" - the absence of STEMI. The confounders for the adjusted regression model were age, gender, glucose, and HbA1C. Statistical processing was performed using IBM SPSS statistics software, version 22.0. The results were considered statistically significant at p < 0.05.

Results

The anthropometric and sociodemographic characteristics of participants are provided in Table 1. The number of men and women in the study was 43.77% and 56.23%, respectively. The mean age of patients in Group 1 was 51 (Q25–75 46–57) and in Group 2–49 (Q25–75 42–55) years old, p = 0.071. The median BMI, WC, systolic, and diastolic blood pressure had no significant differences in the studied groups; however, the median BMI and WC were over normal limits in both groups. Fasting blood glucose did not have statistically significant differences in the groups, comparing the HbA1c, which was significantly higher in patients with pre-diabetes and STEMI (Group 1–6.3 (Q25–75 5.3–6.5) and Group 2–5.7 (Q25–75 5.4–5.9)). The lipid profile also had not statistically significant differences in STEMI and non-STEMI patients.

The values of insulin secretion parameters, incretin hormones, and 1.5-AG showed significant differences between Group 1 and Group 2 (Table 2). The C-peptide value was 1024.2 (Q25–75 733.3–1442.6) ng/ml in the Group 1 and 1221.5 (Q25–75 868.5–1846.4) ng/ml in the Group 2, p = 0.008. Group 1 had a higher insulin level of 11.2 (Q25–75 5.9–26.3) μIU/ml compared with Group 2 where the value was 6.9 (Q25–75 4.3–11.8) μIU/ml, p < 0.001. A similar trend was noted for the HOMA-IR index. Its level in the Group 1 was 2.8 (Q25–75 1.3–7.39), in the Group 2 1.6 (Q25–75 0.9–2.7), p = 0.014.

A higher level of glucagon was noted in patients with STEMI 251.7 (Q25–75 80.5–279.83) ng/ml, whereas, in non-STEMI patients, its concentration was 191.57 (Q25–75 56.7–1305.7) ng/ml, p = 0.003. The GLP-1 concentration had a trend opposite to that of glucagon and was reduced in patients in the Group 1 63.1 (Q25–75 42.4–114.6) ng/ml compared with the Group 2 (80.6 (Q25–7546, 1–98.7) ng/ml), p < 0.001. A similar trend was shown by Ghrelin and GIP; however, their concentrations in the study groups did not differ significantly.

1,5-AG concentration in the Group 1 (301.5 (Q25-75 231.6-393.9) μmol/l) was significantly lower than in the Group 2 (314.6 (Q25-75 250.8-415.1) μmol/l), p = 0.001.

We performed a binary logistic regression study. The STEMI was taken as a response variable. The age, gender, glucose, HbA1c, GLP-1, Ghrelin, GIP, Glucagon, Insulin, HOMA-IR, and 15AG were taken as explanatory variables. The model was also adjusted for age and gender (Table 3).

Table 3: The impact of 1.5-AG on the STEMI odds ratio in patients with pre-diabetes (Binary logistic regression model with covariates)

Variable	B	Mean square error	p-value	Exp (B)	95% confidence interval for EXP (B)	
					Lower	Upper
Gender	−1.915	0.410	0.061	0.597	0.466	0.729
Age	−0.068	0.020	0.074	0.935	1.000	1.008
Glucose	−0.345	0.205	0.093	0.708	0.474	1.060
HbA1c	−0.888	0.532	0.095	0.411	0.145	1.168
GLP-1	−0.026	0.008	0.001	1.775	1.460	1.990
Ghrelin	0.001	0.001	0.079	1.001	1.000	1.002
GIP	−0.001	<0.001	0.085	0.999	0.999	1.000
Glucagon	0.001	<0.001	0.210	1.000	1.000	1.000
Insulin	−0.028	0. 0.026	0.289	0.973	0.924	1.024
HOMA-IR	0.075	0.081	0.351	1.078	0.920	1. 0.263
1.5-AG	0.004	0.002	0,018	2.304	1.980	2.973

The logistic regression shows that a lower plasma concentration of 1.5-AG increases the possibility of STEMI in patients with pre-diabetes [OR 2.304 (95%confidence interval [CI] 1.980–2.973), p = 0.018]. Another significant parameter in the model was GLP-1. Its reduced concentration increased the odds of STEMI [OR 1.775 (95% CI 1.460-1.990), p = 0.001].

Discussion

The results of our study demonstrated a decline of 1.5-AG in patients with pre-diabetes and STEMI. Moreover, adjusted logistic regression analysis showed that decreased 1.5-AG concentration doubled the chance of STEMI in patients with pre-diabetes.

The history of 1.5-AG study has more than two decades. Few studies show a role for 1.5-AG in the prediction of coronary artery disease (CAD). For example, Ikeda *et al*. performed a study of 523 in non-diabetic adults with STEMI in whom the 1.5-AG level was associated with coronary heart disease [14].

A database search did not reveal any completed studies investigating the association between 1.5-AG and acute myocardial infarction in patients with pre-diabetes; however, there are some studies evaluating 1.5-AG in patients with T2DM. The branch of ADVANCE study, which estimated the effect of intensified glucose-lowering therapy on 1.5-AG concentration and clinical outcomes found that 1.5-AG, regardless of HbA1c, can be a risk marker for microvascular events in adults with T2DM [15].

1.5-AG reflects the variability of postprandial glycemia. Although hyperglycemia is undoubtedly associated with increased risk of microvascular and macrovascular complications, the question of the precise mechanism of the impact of various parameters on carbohydrate metabolism is still under investigation. Fasting plasma glucose, postprandial hyperglycemia, and glucose variability all contribute to the balance of the long-term glycemic parameter HbA1c [16].

There is experimental evidence that peaks of postprandial hyperglycemia may have harmful effects on the arterial wall through oxidative stress, endothelial dysfunction, and activation of the blood coagulation cascade [17]. Researchers from Kobe University, Japan, reported that daily glucose fluctuations can affect the coronary atherosclerotic plaque and increase the risk of its rupture in patients with CAD who previously received lipid-lowering therapy [18].

We revealed dyslipidemia in all diabetic patients from our study; however, the parameters of the lipid profile were not associated with STEMI. This fact determines the significant impact of other unconventional markers of cardiovascular events in patients with carbohydrate metabolism disorders.

The decreased GLP-1 concentration in acute myocardial infarction that we obtained in the study emphasizes its clinical significance as a marker of adverse cardiovascular events in patients with pre-diabetes. The protective effects of glucagon and GLP-1 on the heart muscle have been discovered and described earlier. Furthermore, several studies indicate a predictive role of GLP-1 in adverse cardiovascular events. For example, a study by Florian Kahles *et al,* including data from 918 patients with myocardial infarction, revealed its association with GLP-1 concentration in patients without DM [19].

The unique effects of incretins designed the strategy for a whole class of GLP-1 receptor agonists. The studies of adverse cardiovascular outcomes in patients with T2DM proved the cardioprotective effect of GLP-1 receptor agonist and changed approaches to the treatment of patients with diabetes, shifting the focus of therapy from hypoglycemic to cardioprotective [20], [21].

The present research on the effects of incretins on the cardiovascular system of patients with pre-diabetes suggested its changes start earlier than a patient would become hyperglycemic. The randomized controlled trial among adults with metabolic syndrome without diabetes shows that liraglutide plus lifestyle intervention significantly decreased visceral fat. The reduction of visceral adipose tissue may be one instrument to clarify the benefits seen on cardiovascular outcomes in the previous trials among patients with Type 2 diabetes [22]. Studding the secretion of islet prohormones in healthy adults, the authors Ramzy and Kieffer suggest that proinsulin, pro-islet amyloid polypeptide, and proglucagon processing are altered during pre-diabetes and diabetes [23]. The rising glucagon in pre-diabetes patients with STEMI was also discovered in our study.

Insulin and HOMA IR index remain pathogenetic factors of insulin resistance development that grow in patients with pre-diabetes [24], [25]. Several studies highlight their predictive role in the development of adverse cardiovascular events [26].

Our study found that insulin and HOMA IR increased in patients with STEMI compared with patients without STEMI. While the role of insulin resistance as a predictor of cardiovascular events has been shown in a few large studies, according to our data based on the results of logistic regression analysis, no association was found between these markers and STEMI [27], [28]. This can be explained by the fact that the median insulin resistance was just slightly exceeded the reference range for this parameter index in both study groups.

The presented study has some limitations due to the relatively small sample size. In addition, the results may not apply to patients without carbohydrate metabolic disorders.

The result of our study gives us to venture to suggest that low 1.5-AG and GLP-1 may play an important pathogenetic role in the development of myocardial infarction in the cohort of patients with pre-diabetes. Both markers can contribute to the prevention of macrovascular complications in patients with pre-diabetes.

Conclusion

The association between 1.5-AG, GLP-1, and STEMI in patients with pre-diabetes discovered in our study designates their potential role as cardiovascular risk markers in non-diabetic patients with impaired glucose metabolism.

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