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Predictive Model for Acute Heart Failure in Patients with Acute Myocardial Infarction and Type 2 Diabetes Mellitus Based on Energy and Adipokine Metabolism Indicators

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Abstract

BACKGROUND: Acute heart failure (AHF) is one of the early complications of acute myocardial infarction (AMI) in diabetic patients. Evaluation of biomarkers of energy and adipokine metabolism can help in the early identification of diabetic patients at risk of AHF.

AIM: The present study is aimed to predict the development of AHF in diabetic patients with AMI based on energy and adipokine metabolism parameters.

METHODS: A total of 74 diabetic patients with AMI were examined between September 1, 2018, and December 31, 2020. Serum adropin, irisin, and C1q/TNF-related protein 3 (CTRP3) levels were measured by enzyme-linked immunosorbent assay. To predict AHF development in AMI patients, generalized linear mixed model (GLMM) was applied.

RESULTS: The serum concentrations of adropin, irisin, and CTRP3 have been found to be reduced in diabetic patients with AMI and AHF. The accuracy of predicting AHF Killip Class 1 was 96.7%, and the accuracy of prediction for AHF Killip Class 2 was 57.1%, that is, the model was poorly sensitive to this level of complications. The prediction accuracy for AHF Killip Class 3 was 80%, that is, the model was highly sensitive to complications of this level, and for AHF Killip Class 4 – 100% being the maximum level of the model sensitivity.

CONCLUSIONS: Low serum concentrations of adropin, irisin, and CTRP3 indicate an imbalance in energy and adipokine homeostasis. The constructed model predicts the probability of AHF development with high accuracy of 91.9% in diabetic patients with AMI.

Introduction

Acute heart failure (AHF) is one of the early complications of acute myocardial infarction (AMI) in diabetic patients, and despite technological advances in health care, the prevalence of AHF is high and is a serious challenge to the health-care system [1], [2]. Patients with diabetes mellitus (DM) are at increased risk of death and cardiovascular complications than the general population. Diabetic patients had excessive risk of hospitalization for heart failure (HF) [3]. The pathogenetic factors that contribute to HF development at the time of myocardial infarction (MI) hospitalization include compromised myocardium due to myocardial tissue necrosis, myocardial stunning, and mechanical complications. Cardiomyocyte structural changes and edema develop within 30 min of ischemia resulting in progressive cardiac myocyte death after 3 h ischemia. The inflammatory response to myocyte death additionally contributes to HF development [4]. Acute hyperglycemia in patients with ST-segment elevation myocardial infarction (STEMI) may be related to increased systemic inflammation. Worse in-hospital outcomes in patients with STEMI were found to be associated with acute hyperglycemia [5]. Elevated blood glucose level on admission causes increased in-hospital and long-term mortality in patients with STEMI complicated by cardiogenic shock after percutaneous coronary intervention (PCI) [6]. Patients with admission glucose levels over 11.28 mmol/L had significantly higher late mortality compared to those with glucose levels < 11.28 mmol/L. Hyperglycemia is a reliable marker of unfavorable outcome in AMI patients with and without previously diagnosed DM [7]. Among patients with HF with reduced ejection fraction (EF), those with DM had a worse prognosis, including a higher risk of in-hospital intubation, cardiogenic shock, acute kidney injury, intensive care unit (ICU) admission and death during hospitalization, as well as longer ICU and hospital stay [8]. Adropin and irisin are now considered as associated with both AMI and DM markers of energy metabolism influencing the development of AHF in diabetic patients. In a diabetic animal model, irisin overexpression has been shown to increase energy expenditure and improve insulin sensitivity [9]. Cardiomyocytes secrete more irisin than skeletal muscle [10]. Moreover, irisin has been found

to promote cardiac progenitor cell-induced myocardial repair [11]. Increased mitochondrial respiration and oxidative stress due to irisin overexpression and impaired mitochondrial biogenesis could result in HF progression and cardiac fibrosis [12], [13]. It has been demonstrated that serum adropin levels were significantly lower in type 2 DM patients as compared to those in non-diabetic patients and were inversely and independently associated with angiographic severity of coronary atherosclerosis. Hence, it has been suggested that serum adropin could serve as a novel predictor of coronary atherosclerosis [14]. Serum adropin levels were reduced in AMI patients [15]. Further study requires detailed examination of diabetic patients with AMI and AHF based on these markers.

A new anti-inflammatory marker of adipokine metabolism associated with cardiovascular disease is C1q/TNF-related protein 3 (CTRP3). CTRP3 has been shown to be decreased in HF patients with reduced left ventricular (LV) EF and associated with increased morbidity and mortality [16]. Furthermore, serum CTRP3 levels were significantly reduced in 2 type DM patients [17]. Timely identification of patients at risk of AHF and early treatment for diabetic patients with AMI can reduce the mortality rates.

Given the importance of preventing AHF, the aim was to evaluate energy homeostasis (adropin and irisin) and the adipokine system (CTRP3) parameters in diabetic patients with AMI and AHF and to develop a model for AHF prediction in this cohort of patients.

Materials and Methods

The present study was observational, cross-sectional. This study involved 74 diabetic patients with STEMI admitted to the Government Institution "L.T. Malaya National Therapy Institute of the National Academy of Medical Sciences of Ukraine" and the Kharkiv Railway Clinical Hospital No. 1 of the branch "Center of Healthcare" of Public Joint Stock Company "Ukrainian Railway." The study was conducted between September 1, 2018, and December 31, 2020. The Ethics Committee of the Kharkiv National Medical University approved (Protocol No. 2, dated April 2, 2018). Written informed consent was obtained in their native language (Ukrainian).

Inclusion criteria were specified for acute STEMI and type 2 DM: Age ≥ 45 years and diagnosis of AHF. All 74 patients met these criteria.

Cases of diagnosed severe comorbidities type 1 DM, non-ST-elevation AMI, autoimmune diseases, myocardial infarction secondary to functional Class IV chronic heart failure, chronic obstructive pulmonary disease, bronchial asthma, valvular heart disease, symptomatic hypertension, severe liver and kidney dysfunction, severe anemia, bleeding, severe acute respiratory syndrome coronavirus 2, malignancy, and inability to give a written informed consent were excluded from the present study.

We followed the 2017 European Society of Cardiology Guidelines for the diagnosis and management of AMI in patients presenting with ST-segment elevation [18]. Diagnosis and treatment of type 2 DM was based on the joint recommendations of the American Diabetes Association and the European Association for the Study of DM (2018) [19].

Diagnostic testing was carried out in the Biochemical Department of the Central Research Laboratory of Kharkiv National Medical University. Blood serum was collected on day 1 of follow-up and stored at −80°C. Serum total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol were analyzed by peroxidase enzymatic method with assay kits "Cholesterol LiquiColor" (Human GmbH, Germany) and "HDL Cholesterol LiquiColor" (Human GmbH, Germany), respectively. Triglyceride (TG) levels were measured by enzymatic colorimetric method using an assay kit "Triglycerides LiquiColor" (Human GmbH, Germany). The atherogenic index (AI) was calculated by the standard A.M. Klimov formula. The levels of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) were estimated by the Friedewald formula. Fasting blood glucose level was estimated by glucose oxidase method with commercial test system "Human Glucose" (LLC NPP "Filisit-Diagnostics," Ukraine). Calculation of insulin resistance (IR) was achieved by the Homeostasis Model Assessment (HOMA-IR). Serum insulin, adropin, irisin, and CTRP3 levels were measured by enzyme-linked immunosorbent assay with commercial test systems «Human Insulin» (Monobind Inc., USA), Human Adropin» (Elabscience, USA), «Human FNDC5» (Elabscience, USA), and «Human CTRP3» (Aviscera Bioscience Inc., USA), respectively, following the instructions from manufacturers. Normal reference ranges for adropin – 23.58 ± 2.56 pg/mL, irisin – 5.97±2.1 ng/mL, and CTRP3 – 325.97±42.22 ng/mL were determined.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Conventional Doppler echocardiography with an ultrasound scanner "Ultima Pro-30" (LLC "Radmir," Ukraine) was performed.

The data obtained were statistically analyzed using the software package IBM SPPS version 27.0 (2020) (IBM Inc., USA). The following main statistical parameters were calculated: Mean (M) and the standard deviation (SD). Nominal variables were expressed as number and percentage. To test statistical hypotheses in the study, the critical level of significance was considered at $p < 0.05$. To predict AHF development in the study, generalized linear mixed models (GLMMs) were applied.

Results

In our study, the majority of diabetic patients with AMI were male (68.9%), and 83.78% of patients were overweight (Table 1). In AMI patients, the serum concentrations of adropin, irisin, and CTRP3 on day 1 were reduced by 42.11%, 68.84%, and 30.65%, respectively, compared to the identified norms ($p < 0.05$). All the patients presented with hypertension and carbohydrate metabolism abnormalities. Surviving from AHF episodes was noted among all the patients during the follow-up.

Table 1: Basic characteristics of patients

Characteristics	Value: Mean ± SD
Age, years	59.42 ± 7.66
Sex, n (%)	
Male	51 (68.9)
Female	23 (31.1)
Weight, kg	85.54 ± 13.87
Height, cm	171.47 ± 8.02
BMI, kg/m^2	28.88 ± 4.41
Overweight, n (%)	31 (41.9)
Obesity, n (%)	31 (41.9)
Arterial hypertension, n (%)	74 (100)
Previous MI, n (%)	13 (17.6)
AHF, Killip class, n (%)	
1	60 (81.1)
2	6 (8.1)
3	6 (8.1)
4	2 (2.7)
Systolic BP on the 1st day, mm Hg	143.82 ± 29.07
Diastolic BP on the 1st day, mm Hg	83.76 ± 12.35
TC on the 1st day, mmol/L	5.1 ± 1.39
HDL cholesterol on the 1st day, mmol/L	1.13 ± 0.32
AI on the 1st day	3.80 ± 1.70
Platelets×10^9/L on the 1st day	248.50 ± 81.44
Glucose on the 1st day, mmol/L	11.23 ± 4.57
Insulin on the 1st day, μIU/mL	32.51 ± 10.56
HOMA-IR on the 1st day	17.17 ± 11.16
LV EF on the 1st day, %	50.45 ± 9.79
IVST on the 1st day, cm	1.24 ± 0.2
Aortic diameter on the 1st day, cm	3.19 ± 0.42
Adropin on the 1st day, pg/mL	13.65 ± 5.12
Irisin on the 1st day, ng/mL	1.86 ± 0.43
CTRP3 on the 1st day, ng/mL	226.06 ± 52.11

BP: Blood pressure, AHF: Acute heart failure, BMI: Body mass index, CTRP3: C1q/tumor necrosis factor-related protein 3, HOMA-IR: Homeostasis model assessment of insulin resistance, AI: Atherogenic index, HDL: High-density lipoprotein, TC: Total cholesterol, LV EF: Left ventricular ejection fraction, IVST: Interventricular septum thickness, MI: Myocardial infarction, SD: Standard deviation.

AHF Killip Classes I, II, III, and IV were studied as predicted value. Hence, it was *y* for GLMM. A total of 118 indicators were estimated in AMI patients on days 1 and 2. During the first stage, statistically significant correlations between *y* and the measured parameters were revealed, yielding a substantial reduction in the number of possible variables in the GLMM, which are listed in Table 2.

We checked all possible hypotheses and variables in combinations, until we found the best statistically significant model at accuracy of *y* prediction and all its independent variables: Fixed effects (two one-factor and two two-factor indicators) from Table 3 and random effects (seven one-factor indicators) from Table 4.

Discussion

Early identification of a diabetic patient with AMI and HF requires detailed study. Several predictors

Table 2: Parameters selected for generalized linear mixed model

Parameter, units of measurement	Statistical significance (p)	Correlation with *y*
Irisin on the 1st day, ng/mL	0.05	−0.165
Adropin on the 1st day, pg/mL	0.05	0.041
CTRP3 on the 1st day, ng/mL	0.05	−0.081
Platelets×10^9/L on the 1st day	0.05	−0.108
HOMA-IR on the 1st day	0.05	−0.012
Glucose on the 1st day, mmol/L	0.05	0.101
Insulin on the 1st day, μIU/mL	0.05	−0.108
Diastolic BP on the 1st day, mm Hg	<0.05	−0.268
LV EF on the 1st day, %	<0.01	−0.362
AI on the 1st day	0.05	0.028
IVST on the 1st day, cm	0.05	0.092
Aortic diameter on the 1st day, cm	0.05	0.152

AI: Atherogenic index, BP: Blood pressure, CTRP3: C1q/tumor necrosis factor-related protein 3, HOMA-IR: Homeostasis model assessment of insulin resistance, LV EF: Left ventricular ejection fraction, IVST: Interventricular septum thickness.

of HF development in STEMI patients are known today. A powerful predictor of HF was the N-terminal propeptide of natriuretic peptide levels in patients following STEMI (cutoff value of 830 pg/mL) [20]. In patients with AMI and AHF Killip Classes 2–3, lactate levels of more than 2.5 mmol/L were associated with 30-day mortality [21].

Table 3: Parameters showing the fixed generalized linear mixed model effects

Parameters	Statistical significance (p)	Coefficient in GLMM, *X*
One-factor indicators		
LV EF	< 0.001	−0.232
Diastolic BP	0.019	−3.192
Two-factor indicators (combined impact of two-factor indicators)		
Irisin and glucose	0.009	0.464
HOMA-IR and glucose	0.015	−0.025

GLMM: Generalized linear mixed model, LV EF: Left ventricular ejection fraction, BP: Blood pressure, HOMA-IR: Homeostasis model assessment of insulin resistance.

Studies often include type 2 DM in the overall characteristics of the patient cohort with AMI. It is clear, however, that the pathophysiological mechanisms of development and course of AMI in diabetic patients present certain features. Various processes of early AMI complications development in the presence of type 2 DM have to be examined in greater detail.

Table 4: Parameters showing random generalized linear mixed model effects (including only statistically significant effects with P<0.05)

Parameters	Covariations
One-factor indicators	
CTRP3	0.001
Adropin	0.056
Platelets	0.0001
AI	1.044
Insulin	0.004
IVST	20.641
Aortic diameter	7.186

CTRP3: C1q/tumor necrosis factor-related protein 3, AI: Atherogenic index, IVST: Interventricular septum thickness.

Serum irisin concentrations were significantly lower in patients with AMI and HF compared with controls [22]. Decreased irisin concentrations in AMI patients were related to increased secretion of pro-inflammatory factors through activation of signaling pathways: Mitogen-activated protein kinase and extracellular signal-regulated kinase 1 and 2, and thus, the healing process was impaired. The authors found that higher levels of serum irisin were associated with an increased AHF mortality risk [23]. Lower serum adropin levels were measured in AMI patients when compared to patients without coronary artery disease (CAD). It has been reported that patients with severe CAD had low

serum adropin levels compared to those with moderate CAD [24]. Low serum levels of CTRP3 were observed in patients with HF and reduced LV EF [25]. The authors underlined decreased CTRP3 serum levels in patients with CAD, especially in AMI [26], [27].

Nevertheless, findings regarding an adropin deficiency have shown a potent role of this peptide hormone in homeostatic metabolism, realized through regulating insulin sensitivity, avoiding dyslipidemia, and normalizing impaired glucose tolerance [28]. Using an experimental model, improved glucose tolerance and insulin resistance as well as enhanced preferable carbohydrate metabolism over lipid utilization regarding the use energy option have been shown following adropin administration [29]. Plasma adropin levels were lower in atherogenic phenotype than in non-atherogenic profiles, demonstrating a negative correlation with the AI [30]. Studies have found a negative correlation between adropin and HOMA-IR [31] and also between blood insulin levels and CTRP3 [32].

The present study has shown changes in energy and adipokine homeostasis in diabetic patients with AMI in the presence of HF. Low serum concentrations of adropin, irisin, and CTRP 3 have been revealed in patients with STEMI and type 2 DM on 1 day, indicating an imbalance in energy and adipokine metabolism. High prognostic qualities of the constructed model have been pointed out, namely, the accuracy of predicting the AHF Killip Class 1 was 96.7%, and the accuracy of prediction for AHF Killip Class 2 was 57.1%, that is, the model was poorly sensitive to this level of complications. The prediction accuracy for AHF Killip Class 3 was 80%, that is, the model was highly sensitive to complications of this level, while the prediction accuracy for AHF Killip Class 4 reached a 100% rate being the maximum possible level of the model sensitivity to this level of complications. Thus, the AHF prediction model has worked for all Killip classes.

The model demonstrated the advantage of allowing the GLMM method to use at least one random factor with non-stationary levels. The dependent variable linearly related to the fixed factors, random factors, and covariates. The fixed effects simulated the mean dependent variable. The random effects modeled the covariance structure of the dependent variable. Several random effects were considered to be independent of each other, and each one had its own covariance matrix, but the model components given with the same random effect could be correlated. In addition, it was assumed that the dependent variable was taken from the normal distribution.

There was, however, a disadvantage to the model. It tested all possible hypotheses and combined variables to find the best significant model for the prediction accuracy that was time consuming.

Limitations

This study was subjected to several limitations. First, it was the study with a relatively small sample size. Second, given that only type 2 DM patients with AMI were included, AHF development should be further assessed with a focus on testing among non-diabetic patients with AMI. Third, it would be interesting to study diabetic patients with AMI and AHF Killip Class 4, as the model demonstrated 100% of predictions, but that would require a substantial increase in the number of such patients.

In the future, it is planned to examine AMI patients with the presence or absence of type 2 DM on a larger study sample size that requires a longer follow-up period. It would be useful to focus on a separate line of research to study a group of diabetic and non-diabetic AMI patients with Killip Class 4 AHF, which also demands an increase in the sample size and follow-up time for this state.

Conclusions

Low serum concentrations of adropin, irisin, and CTRP3 have been identified in AMI patients with type 2 DM, indicating an imbalance in energy and adipokine homeostasis.

Qualitative analysis of the coefficients at fixed factors of the GLMM has shown that high levels of diastolic BP on day 1 were the strong negative prognostic factor, as well as the value of LV EF in combination with blood glucose and HOMA-IR was also negative factors. The combined effects of irisin and glucose have been identified as the positive prognostic factors.

The constructed statistical model has predicted the probability of AHF development in patients with AMI and type 2 DM with high accuracy of 91.9%.

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