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Predictive model for recurrent myocardial infarction in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Recurrent myocardial infarction (MI) is one of the commonest and serious cardiovascular complications among diabetic patients. This study was planned to predict the recurrent MI development in diabetic patients using parameters of energy and adipokine metabolism. *Methods:* In total, 74 patients with type DM and acute MI were enrolled in the study. Measurements of serum adropin, irisin, fatty acid binding protein 4 (FABP4) and C1q/TNF related protein 3 levels were performed using enzyme-linked immunosorbent assay. The study employed generalized linear mixed models (GLMMs) to predict recurrent MI development. *Results:* The accuracy of predicting the absence of recurrent MI during a year in diabetic patients was 98.4%, and the accuracy of predicting the probability of recurrent MI during a year in diabetic patients was 92.3%. The global model accuracy was 97.3%. *Conclusions*: GLMM has shown that the levels of irisin on day 14, insulin on day 1 and the combined effect of blood glucose on days 1 and 14 were negative prognostic factors. The total impact of FABP4 on day 1, HOMA-IR on day 1 and adropin on day 14 had a positive prognostic value.

Keywords: diabetes, metabolism, myocardial infarction, prognosis

1. INTRODUCTION

Myocardial infarction (MI) and type 2 diabetes mellitus (DM) are the leading causes of mortality and disability worldwide, and the incidence of recurrent MI remains high with a serious risk of complications and death (Furtado et al., 2019; Schmitt et al., 2021). Type 2 DM is a weighty risk factor for coronary heart disease (CHD). Type 2 DM has been found to be linked to a higher risk of recurrent MI (Galasso et al., 2021). Adropin increases glucose utilization by means of fatty acids, improves glucose tolerance, and improves insulin resistance (Jasaszwili et al., 2020). The authors demonstrated that adropin administration helped to improve cardiac function, cardiac efficiency, and coronary blood flow. Besides, measurements of glucose and palmitate involvement in catabolic adenosine triphosphate (ATP) production pathways have shown a central role of adropin in the preferential cardiac glucose oxidation and suppressing cardiac fatty acid oxidation (Altamimi et al., 2019).

DISCOVERY SCIENTIFIC SOCIETY

Myocardial repair stimulated by cardiac progenitor cells has been found to be promoted by irisin (Zhao et al., 2019). Since it is known irisin is released from intact myocytes and other organs to protect the energy stores of ischemic myocardium, it can be hypothesized that diabetic patients with CHD have reduced serum irisin levels due to its insufficient release to meet the demand for further ATP production (Aydin et al., 2014). Fatty acid binding protein 4 (FABP4) is a pro inflammatory adipokine responsible for promoting and maintaining impaired insulin sensitivity and atherosclerosis through both intracellular and extracellular mechanisms (Furuhashi et al., 2019). High circulating FABP4 levels have been found to be significantly correlated with DM, glucose and triglyceride levels. Notably, significantly increased serum FABP4 levels have been shown during the first hours since the onset of acute MI, being a possible indicator of adrenergic overload underlying acute cardiovascular diseases, including acute MI (Obokata et al., 2016).

C1q/TNF related protein 3 (CTRP 3) has been presented as a new anti inflammatory marker involved in adipokine metabolism and associated with cardiovascular disease. To illustrate, patients with stable CHD have been revealed with significantly reduced serum CTRP3 levels (Yildirim et al., 2022). Prevention of CTRP3 inhibition after MI or CTRP3 add on therapy could be a forward looking therapeutic approach to maintain stability and functionality of coronary vessels in the post infarct myocardium, restore cardiac function, and to mitigate a heart failure (HF) phenotype (Yi et al., 2012). The objective of this study, therefore, was to predict the occurrence of recurrent MI in diabetic patients, which could improve the quality of diagnostic and preventive measures for this group of patients.

2. MATERIALS AND METHODS

This cross sectional follow up study included 74 diabetic patients with ST elevation myocardial infarction (STEMI) admitted to the Government Institution “LT Malaya National Therapy Institute of the National Academy of Medical Sciences of Ukraine” and the Kharkiv Railway Clinical Hospital No1 of the branch “Center of Healthcare” of Public Joint Stock Company “Ukrainian Railway”. The study was conducted from September 1, 2018 to March 31, 2022. Inclusion criteria were required for both acute STEMI and type 2 DM: age ≥ 45 years. These criteria were met by all 74 patients. Cases of severe co morbidity diagnosis, namely type 1 DM, non ST-elevation (NSTEMI) acute MI, autoimmune diseases, MI secondary to functional class IV chronic HF, chronic obstructive pulmonary disease, bronchial asthma, valvular heart disease, symptomatic hypertension, severe liver and kidney dysfunction, severe anemia, bleeding, COVID-19, malignancy, inability to give a written informed consent were excluded from this study.

Diagnostic testing was conducted at the Biochemical Department of the Central Research Laboratory. Blood serum samples were prepared on day 1 and 14 of follow up and then stored at 80 ºC. Serum total cholesterol (TC) and high density lipoprotein (HDL) cholesterol were measured by peroxidase enzymatic method with assay kits “Cholesterol Liquicolor” (Human GmbH, Germany) and “HDL Cholesterol liquicolor” (Human GmbH, Germany), respectively. Triglyceride (TG) levels were analyzed by enzymatic colorimetric method using an assay kit “Triglycerides” (Human GmbH, Germany). The atherogenic index (AI) was assessed by the standard AM Klimov formula. The Friedewald formula was used to estimate plasma levels of very low density lipoprotein (VLDL) and low density lipoprotein (LDL). Fasting blood glucose level was detected by glucoseoxidase method with commercial test system “Human Glucose” (LLC NPP "Filisit Diagnostics", Ukraine). “Human Hemoglobin” (LLC NPP "Filisit Diagnostics", Ukraine) test systems were used to quantify whole blood hemoglobin. Calculation of insulin resistance (IR) was realized through the Homeostasis Model Assessment (HOMA-IR). Serum insulin, adropin, irisin, FABP4 and CTRP3 levels were analyzed by enzyme linked immunosorbent assay with commercial test systems “Human Insulin” (Monobind Inc, USA), “Human Adropin», “Human FNDC5”, “Human FABP4” (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, FABP4 – 5, 02±1, 92 ng/mL, CTRP3 – 325.97±42.22 ng/mL were considered.

Body mass index (BMI) was expressed as a fraction with weight in kilograms in the numerator and square meters of height in the denominator. Conventional Doppler echocardiography with an ultrasound scanner Radmir ULTIMA Pro30 (Ukraine) was performed. The statistical examination of the data obtained was realized by the IBM SPPS software package, version 27.0 (2020) (IBM Inc., USA). The following main statistical parameters were computed: Mean (M) and the standard deviation (SD). Nominal variables were presented as number and percentage. The critical level of significance was considered at a value of p less than 0.05 to assumption testing in the study. Prediction of recurrent MI development was realized by applying generalized linear mixed models (GLMMs) to in the study, were.

3. RESULTS

Recurrent MI was considered as predicted value. Therefore, it was *y* for GLMM. Patients with acute MI were tested for 138 indicators on days 1 and 14. Since a case of whether recurrent MI will or will not occur is of the binary character, it seems impossible to construct statistically significant correlations between *y* and the measured indicators. Therefore, it was better to use the method of principal component analysis at the first stage, and thus to select only the indicators with the highest level of extraction. It had the advantage of substantially reducing the number of possible variables in the GLMM model, the list of which is given in Table 1.

The next stage was to sequentially examine all options of the selected variables demonstrated in Table 1 for inclusion or exclusion in the number of fixed and random effects of the model. The criteria for choosing a qualitative statistically justified model were the Akaike information criterion and the Bayesian information criterion along with the total statistical significance of the model and model variables (in this case, $p < 0.05$). Thus, we tested all possible hypotheses and combinations of variables until the best predictive accuracy *y* statistically significant model and its independent variables were found, summarized as fixed effects in Table 2 and random effects in Table 3. So, the fixed (main) effects of the model were represented by two one factor, one two factor and one three factor indicators, and the random effects by seven one factor indicators. The study has identified the share of fixed factors, which are shown in Figure 1. Among the fixed factors, irisin was the most significant, accounting for 40.01%. Let us mention the constructed model performance to prognose: The accuracy of predicting the absence of recurrent MI within a year in diabetic patients was 98.4%, and the accuracy of predicting the probability of recurrent MI within a year in diabetic patients was 92.3%. The overall accuracy of the model was 97.3%.

Table 1 Indicators selected for GLMM

Parameter, units of measurement	Statistical significance	Level of indicator extraction (from 1.0)
HOMA-IR on day 1	$p < 0.05$	0.992
Insulin on day 1, μlU/mL	$p < 0.05$	0.914
Adropin on day 14, pg/mL	$p < 0.05$	0.987
CTRP3 on day 14, ng/mL	$p < 0.05$	0.939
Irisin on day 14, ng/mL	$p < 0.05$	0.961
FABP4 on day 1, ng/mL	$p < 0.05$	0.927
FABP4 on day 14, ng/mL	$p < 0.05$	0.984
Systolic BP on day 1, mm Hg	$p < 0.05$	0.916
Systolic BP on day 14, mm Hg	$p < 0.05$	0.954
Glucose on day 1, mmol/L	$p < 0.05$	0.914
Glucose on day 14, mmol/L	$p < 0.05$	0.954
BMI, kg/m^2	$p < 0.05$	0.877
Aorta diameter on day 1, cm	$p < 0.05$	0.947
Hemoglobin on day 1, g/L	$p < 0.05$	0.822
VLDL on day 1, mmol/L	$p < 0.05$	0.928
TG on day 1, mmol/L	$p < 0.05$	0.971

Note: BP – blood pressure; BMI – body mass index; CTRP3 – C1q/TNF-related protein 3; FABP4 - fatty acid-binding protein 4 HOMA-IR – homeostasis model assessment of insulin resistance; VLDL – very low-density lipoprotein; TG – triglycerides.

Table 2 Indicators representing fixed effects of the GLMM (statistically significant effects with $p<0.05$ are included only)

Parameters	Statistical significance, p	Coefficient in GLMM, *X*
One factor indicators		
Irisin on day 14, ng/mL	$p = 0.005$	-6.96
Insulin on day 1, μlU/mL	$p = 0.004$	-0.369
Two factor indicators (combined impact of two-factor indicators)		
Glucose on day 1 and glucose on	$p = 0.028$	-0.033

day 14, mmol/L		
Three factor indicators (combined impact of three-factor indicators)		
FABP4 on day 1, ng/mL, HOMA-IR on day 1 and adropin on day 14, pg/mL	p = 0.045	0.002

Note: FABP4 fatty acid binding protein 4 HOMA-IR homeostasis model assessment of insulin resistance.

Table 3 Indicators representing random effects of the GLMM (statistically significant effects with p<0.05 are included only)

Parameters	Co variations
One factor indicators	
BMI	0.147
CTRP3 on day 14	0.003
Systolic BP on day 1	0.001
Aorta diameter on day 1	37.59
Hemoglobin on day 1	0.010
VLDL on day 1	157.4
TG on day 1	32.36

Note: BP – blood pressure; BMI – body mass index; CTRP3 – C1q/TNF-related protein 3; VLDL – very low-density lipoprotein; TG – triglycerides.

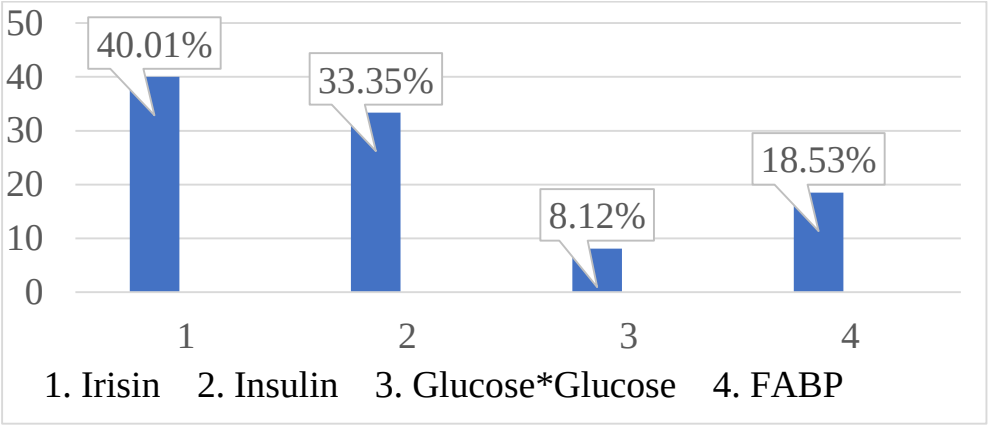

Figure 1 Bar chart showing the share of each fixed factor in the model

4. DISCUSSION

An impartial risk factor for recurrent myocardial infarction is type 2 DM (Li et al., 2016; Lee et al., 2022). Alterations in the lipid profile have shown an association between elevated triglyceride levels and a higher incidence of recurrent MI in patients with plasma LDL <100 mg/dL but not in individuals with LDL ≥100 mg/dL (Suzuki et al., 2019). Both standard biochemical indicators (serum insulin, cholesterol, creatine phosphokinase) and peculiar indicators (plasminogen activator inhibitor type 1 and asymmetric dimethylarginine) were used as predictors for recurrent MI development in the diabetic milieu (the sensitivity of the model was 84.1%, the specificity was 93.1 %, total accuracy 87.7% (Minukhina et al., 2018). However, it is evident, that the pathophysiological mechanisms of recurrent MI development in diabetic patients are characterized by inherent features. Numerous processes underlying MI recurrence in type 2 DM have to be inspected more substantively.

Serum concentrations of irisin have been revealed to be significantly reduced in acute MI patients with HF compared to those in controls (Abd El Mottaleb et al., 2019). Reduced irisin concentrations in acute MI patients were linked to an increased release of pro inflammatory agents via activation of such signaling pathways as mitogen activated protein kinase and extracellular signal regulated kinase 1 and 2, and therefore, the healing mechanisms were compromised. Patients with acute MI demonstrated lower serum adropin levels as compared to those measured in patients without CHD. Besides, severe CHD in patients has been thought to be associated with low serum levels of adropin in contrast to patients with moderate CHD (Ertem et al., 2017). The high correlation has been determined between the highest tertile of FABP4 level and increased risks for recurrent is chemia, MI, stroke, HF, and

peripheral artery disease. Moreover, hypertension, DM, increased systolic blood pressure, along with higher glucose levels have been believed to be associated with an increase in FABP4 circulating levels (Tsai et al., 2021). Finally, the authors have revealed lower serum concentration of CTRP3 in CHD patients, especially in acute MI (Si et al., 2020; Koteliukh et al., 2022). Therefore, the constructed prognostic model predicted the probability of the recurrent MI absence with a high accuracy of 98.4% and the probability of the recurrent MI with an accuracy of 92.3% in patients with 2 types DM within a year based on the measurement findings on the 1st and 14th day of observation. The global model accuracy was 97.3%.

5. CONCLUSION

Qualitative coefficient analysis with fixed factor GLMM has shown that the serum irisin level on day 14 was the strong negative predictor along with the insulin level on day 1 and the combined effects of blood glucose levels on day 1 and day 14 were negative predictors. The total impact of FABP4 on day 1, HOMA-IR on day 1, and adropin on day 14 has given the positive prognostic effect. The probability of recurrent MI in type 2 DM patients has been predicted with the high accuracy of 97.3% by the constructed statistical model.

Limitations

There were some limitations to the study presented. First, given that only patients with acute MI and type 2 DM were included, the occurrence of recurrent MI should be additionally evaluated by focusing on examinations of acute MI patients but without type 2 DM. Second, it would be interested in studying diabetic patients with STEMI and NSTEMI and to examine long term outcomes after acute MI in this patient cohort.

Informed Consent

Written informed consent was obtained in their native language (Ukrainian).

Ethical Approval

The Ethics Commission of the Kharkiv National Medical University approved (Protocol No. 2, dated April 02, 2018).

Author Contributions

Author contributed to all stages of the article.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests

Data and materials availability

All data associated with this study are present in the paper.

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