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Research Article

Interrelation between Insulin Resistance and Clinical Course of Ischemic Etiology Heart Failure in Patients with Prediabetes

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Keywords

- Insulin resistance; Chronic heart failure; Clinical interrelation; Coronary artery disease

Abstract

Background: IR promotes the development of early atherosclerosis and may increase the risk of cardiovascular complications, which is of great importance in patients with CHF. Thus, the assessment of the relationship between IR and clinical indicators of CHF is relevant in the clinical aspect and needs detailed research.

Objective: To evaluate the relationship between IR and clinical parameters in hospitalized ischemic etiology CHF patients without concomitant CMD. Methods. The study included 174 hospitalized patients with a stable course of CHF FC III (NYHA), and CAD from 18 to 65 years old, without previously identified CMD. Anthropological, clinical, laboratory examination was carried out. The neurohormonal profile included insulin (IR by HOMA-IR), aldosterone, and Nt-proBNP levels assessment. To study the relationship of IR with clinical parameters in CHF and CAD patients, a correlation analysis was performed.

Results: A statistically significant relationship between IR and the following parameters was revealed: BMI ($r = 0.186$, $p = 0.045$), total FINDRISC score ($r = 0.386$, $p = 0.000$), SBP ($r = 0.247$, $p = 0.007$), DBP ($r = 0.173$, $p = 0.063$), HbA1c ($r = 0.388$, $p = 0.000$), insulin concentration ($r = 0.833$, $p = 0.000$). To identify independent predictors influencing IR, we carried out multivariate linear regression analysis with stepwise inclusion of indicators in the model, in which HOMA-IR was used as a dependent variable, and BMI, total FINDRISK scores, SBP, DBP, HbA1c levels were included as independent variables. It turned out that the independent factors associated with IR are HbA1c ($\beta = 0.144$; $p = 0.000$) and the FINDRISK scale points ($\beta = 0.064$; $p = 0.05$).

Conclusions: In patients with CHF and CAD, IR is interrelated with such indicators as BMI, FINDRISC total points, SBP, DBP, HbA1c. Independent predictors influencing IR are HbA1c and the FINDRISK total points.

ABBREVIATIONS

BMI: Body Mass Index; CAD: Coronary Artery Disease; CHF: Chronic Heart Failure; CMD: Carbohydrate Metabolism Disorders; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; FC: Functional Class; FINDRISK: The Finnish Diabetes Risk Score; HbA1c: Glycated Hemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin Resistance; Nt-Probnp: N-Terminal Pro-Brain Natriuretic Peptide; NUP: Natriuretic Peptide; NYHA: New York Heart Association; SBP: Systolic Blood Pressure; WC: Waist Circumference

INTRODUCTION

Diabetes and chronic heart failure (CHF), often co-exist with an inter-relationship such that each condition may influence each other in terms of causation and outcome. The Framingham Study highlighted the co-existence of diabetes and CHF [1]. Kannel et al., reported that 19% of patients with CHF in the Framingham Study have diabetes and that the risk of CHF increases by 2-8 folds in the presence of diabetes [1]. The prevalence of diabetes mellitus (DM), is around 4-7% in the general population and 0.5% of the general population has both DM and HF [2,3]. From population-based studies and in CHF trials, the prevalence of T2DM is estimated to be between 11% and 28% and increased to 25-30% among all patients hospitalized for CHF. As stated earlier, there has been a pathophysiological linkage between T2DM and HF. There are numbers of independent risk factors that were identified as predictors of the development of HF in DM. These include increased body mass index (BMI), age, the presence of coronary artery disease (CAD), NYHA functional class FC and glycaemic control measured by glycated hemoglobin (HbA1c) [4-6]. The risk of CHF appears to be related to the blood sugar control in patients with diabetes. Iribarren and colleagues demonstrated that a 1% increase in HbA1C was associated with an 8% increased in risk of CHF independent of blood pressure, BMI, age and presence of CAD [6]. Conversely, the United Kingdom Prospective Diabetes Study showed that a 1% reduction of HbA1c was associated with a 16% reduced risk of developing CHF [7].

The presence of DM is also associated with worse outcome in CHF trials. In the Left Ventricular Dysfunction (SOLVD) trial, DM was an independent predictor of mortality and morbidity in patients in CHF) [8]. Similarly, in the Beta-Blocker Evaluation of Survival Trial (BEST), patients with DM were associated with more severe HF and adverse outcome compared to CHF patients without DM [9]. Held et al. [10], showed each mmol/l increased in fasting plasma glucose in patients with diabetes was associated with a 1.10-fold-increased risk of CHF hospitalization after adjustment for age and sex. All these findings showed a clear and important link between diabetes and CHF. However, we are not certain of the clinical association between IR indicators and parameters in CHF patients. Therefore, the aim of our study was to determine is there an interrelationship between insulin resistance (IR), evaluated by HOMA-IR index and clinical indicators of CHF patients with CAD.

MATERIALS AND METHODS

Study design

We performed correlation analysis to assess the interrelation between IR and clinical parameters in CHF and CAD patients. For determination of independent predictors, influencing on IR multifactorial linear regression analysis was conducted. All patients provided written informed consent.

Study population

In the study, 174 hospitalized CHF patients were included.

Inclusion criteria

Absence of any carbohydrate metabolism disorders (CMD) and glucose-lowering agents in anamnesis, receiving basic CHF therapy (statins, beta-blockers, ACEi/ARB, MRA).

Exclusion criteria

Cognitive impairment, unstable course of CAD, acute heart failure or CHF decompensation, malignancy (receiving active treatment), or other life threatening disease, renal dysfunction (chronic kidney disease class 3b or worse), thyroid dysfunction, pregnancy/lactating females, any other reason considered inappropriate by a study physician, participants who have participated in any other clinical trial within the previous 30 days.

Clinical investigations

Systolic and diastolic blood pressure (SBP and DBP), heart rate, anthropometric indicators (height, weight, BMI and waist circumference (WC)), were assessed. The Finnish Diabetes Risk Score (FINDRISC), questionnaire comprises eight variables: age, BMI, WC, physical activity, daily consumption of vegetables and fruits, antihypertensive drugs use, personal history of hyperglycemia and family history of diabetes. Total score ranging from 0 to 26 points. Subjects scoring ≤ 14 points were considered at «low-moderate risk» and those with > 14 points, at «high risk». These cutoff values have been reported to detect the presence of impaired glucose regulation (prediabetes + unknown DM).

Laboratory Investigations

Fasting and postprandial glucose, HbA1C, lipid profile (total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, nonHDL-C/HDL-C ratio), creatinine (eGFR by CKD-EPI).

Instrumental investigations

12-channel electrocardiography (General Electric Medical System MAC 1200 ST, USA), transthoracic echocardiography with left ventricular ejection fraction (LV EF) evaluation (Philips iE33 xMatrix, Nederlands).

Biomarkers

Neurohormonal profile includes insulin, N-terminal pro-brain natriuretic peptide (Nt-proBNP), and aldosterone levels. Insulin (Vector-Best X-4002, Russia), reference values 1,0-25 mE/l; Nt-proBNP (Vector-Best A-9102, Russia), reference values 20 – 200 pg/ml; aldosterone (BiochemMack, 749-8600, Russia), reference values 10 – 160 pg/ml. IR is estimated by the HOMA-IR = fasting glucose (mmol /L) x fasting insulin (μU / ml) / 22.5. The IR criterion determined the HOMA-IR more than 2.5. ELISA was performed on a Stat Fax 4200, ELISA, Awareness Technology.

Statistical analysis

It is performed using Microsoft STATISTICA 8.0 application. The normality of distribution was determined by the Shapiro-Wilk criterion. To compare the variables with the normal distribution, Student`s t-test was used, the data are presented as mean ± standard deviation (in the form M ± SD, where M is the arithmetic mean, SD is the standard deviation). Variables with nonparametric distribution were compared using Mann-Whitney test, the data are presented as the median (Me (25 and 75 percentile)). The estimation of the correlations between the two variables was carried out using the nonparametric rank coefficient Spearmen. To predict the value of one dependent quantitative variable based on several independent ones, multivariate linear regression analysis was used with stepwise inclusion of indicators into the model. The criterion of statistical significance was the value of $p < 0.05$.

RESULTS AND DISCUSSION

The study included 174 patients with ischemic etiology CHF, whose average age was 62 (57.0-67.0), among them mainly men - 61.5%; 75.9% of patients had arterial hypertension. It should be noted that almost half of the subjects were obese (47.1%), the average BMI was also higher than normal values. The average ejection fraction was 45% (33.0-55.0), the average duration of HF was 4 years. In all patients with CHF of ischemic etiology, along with an increase in aldosterone and Nt-proBNP, there was also an increase in insulin levels. IR was calculated using the HOMA-IR index and was also increased in patients with CHF (Table 1).

To study the relationship of IR with the parameters of patients with ischemic etiology CHF, a correlation analysis was performed (Table 2). A statistically significant relationship between IR and the following parameters was revealed: BMI ($r = 0.186$, $p = 0.045$), total FINDRISC scores ($r = 0.386$, $p = 0.000$), SBP ($r = 0.247$, $p = 0.007$), DBP ($r = 0.173$, $p = 0.063$), HbA1c ($r = 0.388$, $p = 0.000$), insulin concentration ($r = 0.833$, $p = 0.000$), respectively.

To identify independent predictors that affect the indicators of IR, we carried out multivariate linear regression analysis with

Table 1: Clinical characteristics of ischemic etiology chronic heart failure patients.

Indicators	All patients (n=174)
Age (years) *	62,0 (57,0-67,0)
Gender (male, n (%)/female, n (%))	107 (61,5) / 67 (38,5)
Obesity, n (%)	82 (47,1)
Weight (kg) **	81,67±14,9
Waist circumference (sm) *	102,5 (94,0-109,0)
BMI (kg/m^2) *	29,45 (26,4-33,0)
FINDRISC (total points) *	15,0 (12,0-19,0)
Systolic blood pressure (mmHg) *	130,0 (120,0-160,0)
Diastolic blood pressure (mmHg) *	80,0 (70,0-100,0)
Heart rate (beats/min) *	80,0 (70,0-92,0)
Fasting glucose (mmol/l) *	4,7 (4,26-5,17)
Postprandial glucose (mmol/l) *	7,9 (5,7-9,9)
HbA1c (%) *	6,0 (5,5-6,6)
DM heredity, n (%)	38 (21,8)
Smoking, n (%)	44 (25,3)
Arterial hypertension, n (%)	132 (75,9)
Total cholesterol (mmol/l) *	4,24 (3,26-4,9)
Triglycerides (mmol/l) *	1,3 (0,88-1,7)
LDL-C (mmol/l) *	2,39 (1,8-2,99)
HDL-C (mmol/l) *	1,03 (0,9-1,2)
Creatinine (mcmol/l) *	93,5 (84,0-107,0)
eGFR (CKD EPI) (ml/min/1,73m^2) *	70,0 (59,0-82,0)
Ejection fraction (%) *	45,0 (33,0-55,0)
HF duration (years) *	4,0 (2,0-6,0)
Insulin (mMU/l) *	61,8 (54,6-74,1)
HOMA-IR *	14,06 (10,9-18,2)
Aldosterone (pg/ml) *	248,06 (184,9-309,7)
Nt-proBNP (pg/ml) *	1220,4 (437,7-2938,5)

Abbreviations: * - data presented as Me (25%-75%); ** - data presented as M±SD; BMI – body mass index; FINDRISC – the Finnish diabetes risk score; LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate, CKD-EPI-Chronic Kidney Disease-Epidemiology; HOMA-IR – Homeostasis Model Assessment of Insulin Resistance); Nt-proBNP – N-terminal pro-brain natriuretic peptide.

step-by-step inclusion of indicators in the model. A model was formed in which the HOMA-IR index was used as a dependent variable, and BMI, total FINDRISK scores, SBP, DBP, and HbA1c levels were included in the model as independent variables. When analyzing the results obtained, it turned out that the independent factors associated with IR in the studied population are: HbA1C (β = 0.144; p = 0.000), and the total number of points on the FINDRISK scale (β = 0.064; p = 0.05) (Table 3).

DISCUSSION

The main pathogenetic link in the development of CMD is IR, which is one of the key mechanisms for the development and progression of CHF. IR disrupts the functioning of the myocardium due to pathological mechanisms such as endothelial dysfunction, inflammation and oxidative stress, remodeling and impaired myocardial metabolism [11].

In 2010, Dutch scientists evaluated the relationship of neurohormonal status in patients with CHF with and without CHF and examined 371 patients with the determination of the levels of 10 neurohormones - norepinephrine, adrenaline, dopamine, aldosterone, renin, endothelin, atrial natriuretic peptide (NUP), N-terminal atrial NUP, brain NUP and Nt-proBNP [12]. At baseline, patients were comparable in age, left ventricular ejection fraction, severity and etiology of CHF. According to the

Table 2: Correlation analysis between HOMA-IR and clinical, laboratory parameters of ischemic etiology heart failure patients.

Indicator	r	*P*
HOMA-IR and age	0,057	0,540
HOMA-IR and waist circumference	0,060	0,522
HOMA-IR and BMI	0,186	0,045 *
HOMA-IR and FINDRISK	0,386	0,000 *
HOMA-IR and SBP	0,247	0,007 *
HOMA-IR and DBP	0,173	0,063 *
HOMA-IR and heart rate	-0,036	0,701
HOMA-IR and HbA1c	0,388	0,000 *
HOMA-IR and TC	0,035	0,707
HOMA-IR and TG	0,105	0,272
HOMA-IR and LDL-C	0,030	0,748
HOMA-IR and HDL-C	0,054	0,570
HOMA-IR and creatinine	-0,069	0,459
HOMA-IR and eGFR	-0,056	0,547
HOMA-IR and insulin	0,840	0,000 *
HOMA-IR and aldosterone	0,008	0,926
HOMA-IR and Nt-proBNP	-0,051	0,586
HOMA-IR and ejection fraction	0,148	0,112
HOMA-IR and HF duration	-0,134	0,150

Abbreviations: r – Spearmen correlation; * - p<0,05; HOMA-IR – Homeostatic Model Assessment of Insulin Resistance; BMI – body mass index, FINDRISC – the Finnish diabetes risk score, SBP – systolic blood pressure, DBP – diastolic blood pressure, HBA1c – glycated hemoglobin, TC – total cholesterol, TG – triglycerides, LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate, Nt-proBNP – N-terminal pro-brain natriuretic peptide; HF – heart failure.

Table 3: Multivariate linear regression analysis (HOMA-IR and clinical, laboratory parameters of ischemic etiology heart failure patients).

Indicator	β	p
	R^2 = 0,119 F = 3,112 p < 0,002	
Body mass index	-	-
FINDRISK	0,195	0,04
Systolic blood pressure	-	-
Diastolic blood pressure	0,102	0,277
HbA1c	0,199	0,038

Abbreviations: β – multiple regression coefficient, R^2 – coefficient of determination, F – Fisher`s test, p - reliability of multiple regression coefficient

results of the study, statistically significant differences in the activation of neurohormonal systems in patients with CHF were revealed only for brain NUP, while the levels of other hormones did not differ significantly. The results obtained can be associated with a non-standardized approach to therapy, as well as with the use of hypoglycemic agents of various properties in the group with diabetes.

With regard to hyperactivation of sympathetic nervous system, a study was carried out in 2016, the purpose of which was to identify the relationship between blood pressure and IR, WC and BMI in adults. The study revealed a significant relationship between BMI and IR. It should be noted that this relationship was stronger in the group with increased blood pressure. A relationship has also been identified between HOMA-IR and WC. Logistic regression showed that HOMA-IR is a predictor of unstable blood pressure (OR 2.0, h = 0.001) [13].

Previous reports have documented that FINDRISK is more strongly related to IR than to impaired insulin secretion, as confirmed in a study including 7232 Finnish men. Since most of the times IR precedes DM diagnosis the FINDRISK might be useful in identifying the disease at an early stage. Moreover, it has been shown, that FINDRISC`s ability to detect IR is even greater than its ability to identify previously undiagnosed DM, thus increasing its clinical relevance [14].

CONCLUSION

The development of IR in patients with CHF of ischemic etiology, as well as the presence of a relationship with certain clinical parameters, makes it possible to postulate the possibility and necessity of detecting early CMD in patients with CHF, taking into account the identified independent predictors affecting IR. Thus, with the correct organization of screening in groups of patients with a high probability of early detection of early CMD, timely treatment at the stage of prediabetes can significantly reduce the development of diabetes in patients with CHF and reduce the economic burden on health care.

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