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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Angiographic severity of coronary artery disease and cardiovascular risk in acute coronary syndrome in patients with metabolic syndrome

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Abstract

Background: The extent of angiographic lesions, size of infarct, and in-hospital and long-term prognosis in patients with metabolic syndrome (MS) have not been clearly determined.

Aim: The aim of the study was to investigate the effect of MS on the severity of coronary artery disease (CAD) and cardiovascular risk evaluated using the GRACE 2.0 risk score and left ventricular ejection fraction (LVEF) in patients with first acute coronary syndrome (ACS) treated with coronary angioplasty.

Methods: The study was conducted in a group of 160 consecutive patients hospitalised for their first ACS. Coronary angiography was assessed and an echocardiographic evaluation of LVEF was performed. MS was diagnosed according to the National Cholesterol Education Programme-Adult Treatment Panel III criteria. Cardiovascular risk was evaluated using the GRACE 2.0 score. Statistical analysis was performed using the STATISTICA software version 12.0.

Results: Diagnostic criteria for MS were met by 53.5% of the patients. Patients with and without MS did not differ in angiographic severity of CAD and cardiovascular risk as evaluated with the GRACE 2.0 score. LVEF was significantly elevated in patients with MS. In the examined group the angiographic severity of CAD correlated positively with age, body mass index (BMI) and the homeostatic model assessment for insulin resistance (HOMA-IR) index. The cardiovascular risk correlated positively with age, BMI, fasting insulin levels, and HOMA-IR, and inversely with blood pressure and triglyceride levels. The multivariable regression model for predicting the LVEF value indicated that the strongest prognostic factor was the type of ACS.

Conclusions: The associations between the angiographic severity of CAD and age, BMI, and insulin resistance (IR) confirm the involvement of these parameters in coronary atherosclerosis. The correlations between the estimated cardiovascular risk and IR indicate the prognostic value of metabolic parameters in patients after first ACS. The type of ACS is the strongest predictor of LVEF at discharge in this population.

Key words: acute coronary syndrome, metabolic syndrome, angiographic assessment of coronary arteries, cardiovascular risk, GRACE risk score, left ventricular ejection fraction

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INTRODUCTION

Atherosclerotic coronary disease, as well as atheromatous plaque progression and rupture with subsequent thrombosis, play a key role in the pathogenesis of acute coronary syndrome (ACS) [1]. The classic risk factors for coronary artery disease (CAD) include age, male sex, sedentary lifestyle, and smoking, but also components of metabolic syndrome (MS) [2, 3]. The extent of angiographic lesions, size of infarct, and in-hospital and late prognosis in patients with MS have not been clearly determined. There have been only a few studies regarding this issue, with conflicting results [3–8]. As part of MS, insulin resistance (IR) is an important risk factor for the

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development of cardiovascular disorders. It is associated with poor prognosis in the setting of acute myocardial infarction [9]. Moreover, clinical and experimental studies revealed an association between IR and myocardial and microvascular injuries after ST-segment elevation myocardial infarction (STEMI) [10–12]. Undoubtedly, in-depth knowledge about markers of ACS, including those affecting early and late prognosis, is important for good clinical decision making in the prevention and therapy.

The most popular tool used to improve the selection of patients with worse prognosis and optimise the therapy is the GRACE 2.0 risk score. It allows an estimation of the risk of in-hospital death, post-discharge death within six to 12 months, and death or another acute cardiac episode within 12 months after discharge [13]. Another important prognostic parameter in patients after ACS is left ventricular ejection fraction (LVEF). It has been proven that left ventricular functional impairment is an important predictor of increased mortality after ACS [14].

The aim of the study was to compare the severity of CAD and the cardiovascular risk evaluated using the GRACE 2.0 risk score and LVEF, depending on the occurrence of MS, in patients with first ACS treated with coronary angioplasty.

METHODS

The study was conducted in a group of 160 consecutive patients of the Cardiology Department of Pomeranian Medical University in Szczecin, hospitalised for their first ACS, treated with coronary angioplasty. The age of patients ranged from 18 to 70 years. The research protocol was approved by the Bioethics Commission of Pomeranian Medical (no. KB-0080/150/09).

The exclusion criteria were as follows: age over 70 years, lack of the patient's consent for participation, fibrinolytic treatment, chronic anticoagulant treatment, active inflammation, diagnosed kidney disease or cancer, insulin-dependent diabetes, and history of stroke.

The initial diagnosis of ACS, established on the basis of symptoms and electrocardiographic findings, was confirmed by the presence of markers of myocardial necrosis (cardiac troponin I, creatinine kinase-MB) according to current standards [15]. Standard echocardiography was performed. All patients underwent coronary angiography as a routine procedure before angioplasty. Before discharge from hospital echocardiographic evaluation of the left ventricular function was performed using the GE VIVID E9 (General Electric, Boston, MA, USA) apparatus with the sector probe at a frequency of 1.5–4.6 MHz.

In all patients MS was evaluated according to the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP ATP III) criteria [16]. For further analysis, the patients were divided into two groups: with and without metabolic syndrome (MS+ and MS–, respectively).

On the day of hospital admission, blood samples were taken from the patients to determine the levels of sodium, potassium, and creatinine, as well as the presence of cardiac necrosis markers. The levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were determined within the first 24 h after admission. Fasting blood samples to determine glucose and insulin levels were obtained on the fourth day of hospitalisation. The homeostatic model assessment for insulin resistance (HOMA-IR) index was calculated by the following formula: fasting insulin concentration × fasting glucose concentration / 22.5. Laboratory investigations were performed with the use of commercially available assays.

On the basis of the obtained data, cardiovascular risk was evaluated for all patients according to the GRACE 2.0 risk score, using a computer calculator available on the GRACE 2.0 website (www.gracescore.org).

Statistical analysis

For statistical analysis, STATISTICA software version 12.0 from StatSoft Inc. was used. Normal distribution was checked with the Shapiro-Wilk test. When comparing differences in assessed variables, the Student t-test was used when normal distribution was followed, and the Mann-Whitney U test or the Kruskal-Wallis test (or both) was used in case of non-normal distribution. Categorical variables were analysed using the χ^2 Pearson test or the Fisher exact test as appropriate. The Spearman rank test was used to assess correlations. Quantitative variables were presented as median and minimal and maximal values. The analysed qualitative variables were expressed as number (n) and percentage (%). A p-value of less than 0.05 was assumed as statistically significant. The effect of selected variables on LVEF at discharge was analysed using a multivariable regression model.

RESULTS

Clinical and angiographic characteristics of the patients are presented in Table 1.

The diagnostic criteria for MS were met by 53.5% of the patients. The clinical and angiographic variables of the MS+ and MS– groups are compared in Table 2.

Patients did not differ in angiographic severity of CAD and cardiovascular risk as evaluated with the GRACE 2.0 risk score. In the MS+ group, LVEF was significantly elevated as compared with the MS– group. The presence of MS did not significantly affect the distribution of various ACS types (Table 3).

In the whole study group, the angiographic severity of CAD expressed as the epicardial artery affected correlated positively with age, body mass index (BMI), fasting insulin levels, and HOMA-IR (Table 4).

Cardiovascular risk assessed with the GRACE 2.0 risk score correlated positively with age, BMI, fasting insulin levels,

Table 1. Characteristics of the study group

Variable	Number (percentage)
Women (age: median 59 years; min–max 33–70 years)	32 (20%)
Men (age: median 55 years; min–max 33–70 years)	128 (80%)
Smokers	104 (65%)
Hypertension	64 (40%)
Hypercholesterolaemia	29 (18.1%)
Metabolic syndrome	86 (53.8%)
Angiographic profile of CAD:	
SVD	88 (55%)
DVD	56 (25%)
TVD	16 (10%)
ACS type:	
UA	20 (12.5%)
NSTEMI	28 (17.5%)
STEMI	112 (70.0%)
Cardiac arrest	2 (1.3%)
Killip class:	
I	140 (87.5%)
II	16 (10%)
III	4 (2.5%)
IV	0 (0%)
PCI of:	
LMS	1 (0.6%)
LAD	64 (40.6%)
LCX	29 (18.1%)
RCA	61 (38.1%)
LAD and LCX	2 (1.3%)
RCA and LCX	2 (1.3%)

Data are shown as number (percentage). ACS — acute coronary syndrome; CAD — coronary arterial disease; DVD — double vessel disease; LAD — left anterior descending artery; LCX — left circumflex artery; LMS — left main coronary artery; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; SVD — single-vessel disease; TVD — triple-vessel disease; UA — unstable angina

and with HOMA-IR, and negatively with systolic blood pressure, diastolic blood pressure, and triglyceride levels (Table 5).

The results of the multivariable regression model for the prognostic value of decreased LVEF at discharge are presented in Table 6. The model demonstrated that the strongest prognostic marker was the type of ACS (STEMI-ACS, $\beta = -0.34$, $p < 0.001$). Other significant independent prognostic factors of decreased LVEF at discharge included heart rate Killip class, HDL-C levels, positive family history of cardiovascular diseases, and the presence of MS. Their strength expressed with a β factor was similar. In the case of HDL-C concentrations, an inverse relationship was observed — for each additional 1 mg/dL of HDL-C the LVEF was lower by 0.13%. The presence of MS increased the value of LVEF at discharge by almost 3%, similarly to the disease burden in family history. For each class in the Killip classification, the LVEF decreased by nearly 3%.

DISCUSSION

In this clinical cross-sectional study, we compared patients with and without ACS in terms of the clinical course of the first ACS and prognosis after ACS. It should be emphasised that diagnosing MS during an acute event is difficult because pathophysiological and psychological stress associated with acute coronary episodes affects the components of MS, such as glucose and lipid concentrations or blood pressure. Because of the above limitations in diagnosing MS during ACS, few clinicians assess its prevalence and the results mainly come from retrospective analyses of national databases [17].

Due to an association between endogenous insulin concentrations and IR, we decided to exclude patients with diabetes treated with insulin before hospital admission. Such an approach allowed us to compare the course of ACS in patients with and without MS, as well as assess a correlation between early reversible markers of MS, such as IR, angiographic severity of CAD, and cardiovascular risk after ACS. Overt diabetes is included in the diagnostic criteria for MS, although the usefulness of diagnosing MS in patients with type 2 diabetes is criticised in the available literature [18], particularly because of the high prevalence of MS in patients with type 2 diabetes (ca. 75%). The present study has demonstrated that cardiovascular risk in diabetic patients with MS is not higher than the sum of risks related to its individual components [19].

In our own study the risk of MS was about 53.8% and was significantly higher than the value of 20–30% observed in the general population [20]. Interestingly, in patients with MS, despite a significantly higher BMI and more severe metabolic disorders, the first acute coronary incident occurred at a significantly older age compared with those without MS. Moreover, the estimated risk of in-hospital death as well as death within six and 12 months after ACS measured with the GRACE 2.0 risk score, was comparable to that in patients without MS. It could be explained by the so called "obesity paradox" in cardiovascular diseases. Currently, it is believed that BMI has no effect on life expectancy in patients after myocardial infarction [21, 22]. Epidemiological studies demonstrated that obesity is correlated with an increased incidence of diabetes, arterial hypertension, and cardiovascular diseases, so it is associated with increased rates of cardiovascular mortality [23]. However, some recent studies have documented a protective effect of overweight and obesity in patients with CAD who underwent revascularisation and in those with acute coronary disease or heart failure. This phenomenon has been termed an "obesity paradox" [24, 25]. Several hypotheses have been

Table 2. Characteristics of patients with acute coronary syndrome according to the presence of metabolic syndrome (MS+) or absence of metabolic syndrome (MS–)

Variable	MS+ (n = 86) Median (min–max)	MS– (n = 74) Median (min–max)	p
Age [years]	58 (33–70)	54 (36–70)	< 0.05
Body mass index [kg/m^2]	28.0 (23.1–35.9)	25.3 (20.9–37.2)	< 0.001
Waist circumference [cm]	106.5 (72.0–139.0)	94.0 (70.0–140.0)	< 0.001
Systolic BP [mmHg]	150 (100–220)	140.0 (80–190)	< 0.05
Diastolic BP [mmHg]	85 (60–120)	80 (60–120)	NS
Heart rate [/min]	76.5 (50–112)	70 (40–120)	< 0.05
Fasting plasma glucose [mg/dL]	102 (75–178)	94.3 (72–160)	< 0.001
Fasting insulin [μU/mL]	16.6 (3.4–35.9)	12.1 (3.6–29.8)	< 0.001
HOMA-IR	4.52 (0.8–13.5)	2.85 (0.82–8.23)	< 0.001
Total cholesterol [mg/dL]	219.5 (107–373)	203.5 (117–322)	NS
HDL [mg/dL]	39.0 (25.0–84.0)	49.0 (30.0–87.0)	< 0.001
LDL [mg/dL]	153.5 (48.0–288)	131.5 (52.0–258)	NS
Triglyceride [mg/dL]	176.5 (59.0–625)	107.5 (40.0–186.0)	< 0.001
Serum creatinine [mg/dL]	0.9 (0.6–2.15)	0.85 (0.54–1.21)	NS
eGFR [mL/min]	94.0 (32–123)	97.0 (54.0–157.0)	< 0.05
Angiographic severity of CAD	1 (1–3)	1 (1–3)	NS
GRACE 2.0 IH D %risk	0.9 (0.2–17.0)	0.8 (0.1–12.0)	NS
GRACE 2.0 6M D %risk	2.4 (0.7–25.0)	1.9 (0.6–16.0)	NS
GRACE 2.0 1Y D %risk	2.4 (0.7–33.0)	1.9 (0.6–16.0)	NS
GRACE 2.0 1Y D/MI %risk	5.95 (3.40–39.0)	5.35 (2.40–25.0)	NS
LVEF [%]	55.0 (30–70)	50.1 (20–65)	< 0.005

Data are shown as median (min–max). BP — blood pressure; eGFR — estimated glomerular filtration rate; CAD — coronary artery disease; GRACE 2.0 IH D%risk — percentage risk in-hospital mortality calculated with GRACE 2.0 risk score; GRACE 2.0 6M D % risk — percentage risk of six-month mortality calculated with the GRACE 2.0 risk score; GRACE 2.0 1Y D %risk — percentage risk of one-year mortality calculated with the GRACE 2.0 risk score; GRACE 2.0 1Y D/MI %risk — percentage risk of mortality or repeat myocardial infarction within one year calculated with the GRACE 2.0 risk score; HOMA-IR — the homeostasis model assessment of insulin resistance; LDL — low-density lipoprotein; HDL — high-density lipoprotein; LVEF — left ventricular ejection fraction; NS — not statistically significant

Table 3. Distribution of acute coronary syndromes depending on the occurrence of metabolic syndrome (MS); $\kappa^2 = 0.93$ — non-significant

	MS+	MS–	Total
Unstable angina	10 (50%)	10 (50%)	20 (100%)
NSTEMI	15 (53.6%)	13 (46.4%)	28 (100%)
STEMI	61 (64.5%)	51 (45.5%)	112 (100%)
Total	86 (100%)	74 (100%)	160 (100%)

Data are shown as number (percentage). NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

postulated to explain this paradox: 1) the frequency of chronic diseases that reduce body weight increases with age, 2) obese patients are diagnosed earlier and are more effectively treated due to numerous risk factors as compared with slim persons who "feel healthy" and do not take treatment, which has an effect both on the clinical course of ACS and prognosis after ACS; 3) haemodynamic theory presumes that obese patients have "wider and larger" vessels compared with slim persons, and 4) hypodermic fat tissue has a protective effect on the cardiovascular system, in contrast to visceral fat [26–28].

The significant positive correlation between angiographic severity of CAD and age, BMI, and IR in all our patients with the first ACS suggests that the above parameters are involved in the development of stenosis in coronary arteries. The

Table 4. Correlations between angiographic severity of coronary artery disease and clinical and laboratory parameters

Angiographic severity of the coronary disease	N = 160	
	r	p
Age [year]	0.26	< 0.005
Body mass index [kg/m^2]	0.17	< 0.05
Systolic BP [mmHg]	0.10	NS
Diastolic BP [mmHg]	0.04	NS
Total cholesterol [mg/dL]	–0.02	NS
LDL [mg/dL]	–0.02	NS
HDL [mg/dL]	–0.06	NS
Triglyceride [mg/dL]	0.01	NS
eGFR	–0.01	NS
Fasting insulin [μU/mL]	0.28	< 0.001
HOMA-IR	0.30	< 0.001

BP — blood pressure; eGFR — estimated glomerular filtration rate; HDL — high-density lipoprotein; HOMA-IR — homeostatic model assessment for insulin resistance; LDL — low-density lipoprotein; r — correlation coefficients; NS — not statistically significant

results of our study are consistent with those reported in the literature [4–7].

In the whole study group assessed using the GRACE 2.0 score, the cardiovascular risk after ACS, both in-hospital and in the long-term follow-up, correlated positively with HOMA-IR, which indicates a significant association of IR with early and long-term prognosis after ACS. This finding is corroborated by a study of Trifunovic et al. [9] who demonstrated that IR assessed by the HOMA-IR index during the acute phase of the first anterior STEMI in patients without diabetes treated by primary percutaneous coronary intervention is independently associated with poorer myocardial reperfusion,

Table 5. Correlations between cardiovascular risk evaluated using the GRACE 2.0 score and clinical and laboratory parameters

Parameters	N = 160	
	r	p
Risk of in-hospital death:		
Age [year]	0.60	< 0.001
BMI [kg/m^2]	0.28	< 0.001
Systolic BP [mmHg]	–0.43	< 0.001
Diastolic BP [mmHg]	–0.40	< 0.001
Triglyceride [mg/dL]	–0.28	< 0.001
Fasting insulin [μU/mL]	0.33	< 0.001
HOMA-IR	0.31	< 0.001
Risk of death within six months after ACS:		
Age [year]	0.67	< 0.001
BMI [kg/m^2]	0.29	< 0.001
Systolic BP [mmHg]	–0.30	< 0.001
Diastolic BP [mmHg]	–0.30	< 0.001
Triglyceride [mg/dL]	–0.22	< 0.005
Fasting insulin [μU/mL]	0.31	< 0.001
HOMA-IR	0.30	< 0.001
Risk of death or repeat myocardial infarction within one year:		
Age [year]	0.46	< 0.001
BMI [kg/m^2]	0.28	< 0.001
Systolic BP [mmHg]	–0.28	< 0.001
Diastolic BP [mmHg]	–0.27	< 0.001
Triglyceride [mg/dL]	–0.16	< 0.05
Fasting insulin [μU/mL]	0.28	< 0.001
HOMA-IR	0.34	< 0.001

ACS — acute coronary syndrome; BMI — body mass index; BP — blood pressure; HOMA-IR — homeostatic model assessment for insulin resistance; r — correlation coefficients

Table 6. Analysis of simultaneous effect of selected variables on the left ventricular ejection fraction height at discharge in a multiple regression model (multiple R2 = 0.33, constant term = 67.02)

Dependent variable	Parameter	P	β (95% CI)
Sex	–1.11	NS	–0.05 (–0.19 to 0.08)
Age [year]	0.12	NS	–0.19 (–0.33 to –0.05)
Heart rate [/min]	–0.11	< 0.05	–0.20 (–0.34 to –0.05)
Killip class	–2.94	< 0.05	–0.15 (–0.29 to 0.00)
HDL [mg/dL]	–0.13	< 0.05	–0.19 (–0.34 to –0.04)
Genetic predisposition toward CVD	3.07	< 0.05	0.16 (0.03 to 0.30)
MS (+)	2.85	< 0.05	0.17 (0.01 to 0.33)
STEMI	–6.23	< 0.001	–0.34 (–0.47 to –0.20)

CI — confidence interval; CVD — cardiovascular diseases; HDL — high density lipoprotein, MS — metabolic syndrome; NS — not statistically significant; STEMI — ST-segment elevation myocardial infarction

impaired coronary microcirculatory function, and potentially with larger final infarct size. In our study, the GRACE 2.0 score correlated with age, blood pressure, and estimated glomerular filtration rate because these parameters are components of the score itself.

Interestingly, our regression analysis confirmed that the value of LVEF at discharge in patients with ACS was slightly, but significantly, higher in patients with MS. After adjustment for sex and age, the following factors predicted LVEF at discharge in as many as 33% of cases: the type of ACS, heart rate, Killip class, HDL-C concentrations, familial predisposition to cardiovascular diseases, and the occurrence of MS. The strongest prognostic factor for LVEF was the type of ACS. In the case of STEMI, the LVEF decreased by 6.23%. Conversely, the presence of MS increased the LVEF values at discharge by nearly 3%.

To our knowledge, we are the first to report a positive prognostic value of LVEF in patients with MS and the first ACS. Therefore, we cannot compare our results with those reported by other authors. We may only speculate that patients with MS have a constellation of quite easily modifiable factors, which ensure a higher LVEF. In patients without MS who have suffered ACS, we cannot exclude the presence of adverse, non-modifiable genetic mechanisms that lead to larger left ventricular injury following ACS. Further studies are needed to confirm these findings.

Limitations of the study

Our study has several limitations. Firstly, it included only cardiovascular risk assessment, instead of the actual risk assessment. Although the GRACE risk calculator is widely used and accepted, it allows only an estimation of risk. Another limitation is a relatively small number of patients. Moreover, the age restriction could contribute to a lower percentage of female participants. Finally, the exclusion of patients with type 2 diabetes treated with insulin before hospital admission enabled an evaluation of endogenic insulin levels and IR on the one hand, but on the other hand, such an approach might have resulted in the inclusion of a higher percentage of patients without MS.

CONCLUSIONS

The observed correlations between angiographic severity of CAD and age, BMI, and IR confirm the involvement of these parameters in the development of coronary atherosclerosis. The correlations between cardiovascular risk, estimated using the GRACE score, and IR confirm the prognostic value of metabolic parameters in patients after their first ACS. The most useful markers for the prediction of LVEF at discharge in patients with the first ACS include the type of ACS, followed by the presence of MS, heart rate, Killip class, HDL-C concentration, and genetic predisposition to cardiovascular diseases.

Conflict of interest: *none declared*

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