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OBESITY AND DIABETES MELLITUS AS RISK FACTORS OF ONE YEAR MORTALITY IN PATIENTS WITH UNSTABLE ANGINA

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Abstract: *The short term prognosis of patients with unstable angina is determined by the severity of ischemia and of the coronary disease, and on the long term by the intervention of the cardiovascular risk factors. Recent published data, shows controversial results between the influence of obesity and glicate hemoglobin on the prognosis of patients with acute coronary syndromes. This observational and prospective study evaluates the influence of cardiovascular risk factors in 140 patients hospitalized for unstable angina on the mortality risk during one year of surveillance. The risk of death in patients with unstable angina at one year follow-up, was significantly influenced by age over 75 years, previous documented coronary heart disease, diabetes mellitus, high plasma values of glicate hemoglobin (Hb1Ac) and low values of estimated glomerular filtration rate (eGRF). The high body mass index and the waist circumference did not correlate with the risk of death at the one year follow-up of patients with unstable angina.*

Key words: *obesity, diabetes mellitus, cardiovascular events, unstable angina.*

1. Introduction

The long and short term prognosis of unstable angina as a form of acute coronary syndromes (ACS) without ST segment elevation can be evaluated using the GRACE and C-ACS risk score models [10], [12]. In both score models, the acute cardiac dysfunction and hemodynamic instability, influenced by the severity of ischemia and burden of coronary artery disease, provide consistent points to asses the risk of death.

Frequently the clinical features of patients with unstable angina, do not include signs of hemodynamic instability and in these patients, the long term prognosis is determined by the intervention of cardiovascular risk factors.

The known cardiovascular risk factors such as arterial hypertension, diabetes, dislipidemia, smoking, family history of

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early onset coronary heart disease, obesity, hyperhomocysteinemia and some other unconventional risk factors like inflammation, malnutrition, anemia, high levels of urinary albumin and the decrease of arterial elasticity, influence the evolution of patients with unstable angina [15], [21], [23].

There are conflicting literature data regarding the influence of obesity on the evolution of clinically stable patients with unstable angina.

In 2011 the data collected from a "systematic review of the literature" found that in patients with ACS, the central obesity, estimated by waist circumference, but not normal or high body mass index (BMI), were directly associated with higher mortality [25]. The "obesity paradox", which means low mortality risk associated with high, rather than normal or low BMI, was described in patients with ACS. This phenomenon was initially attributed to residual confounding factors [3], [25].

Numerous studies related to the correlation between diabetes mellitus and coronary artery disease revealed that diabetic patients compared to non-diabetic, have a higher risk of cardiovascular death due to a higher extent and severity of atherosclerotic coronary lesions [4]. It was also demonstrated that in patients with ACS the presence of diabetes mellitus is associated with an increased risk of death [19]. In patients with unstable angina and diabetes mellitus, there is an increased risk of myocardial infarction and cardiovascular death [11].

2. Objective

The aim of the study was to evaluate the impact of obesity and uncontrolled diabetes mellitus on the one year mortality rate in patients with unstable angina.

3. Materials and Methods

The study group included 140 patients, admitted with unstable angina in the Coronary Unit of Clinical County Emergency Hospital of Brasov, from June 2013 to June 2014.

The diagnosis of unstable angina was established using the criteria of the European Society of Cardiology Guidelines on the management of Acute Coronary Syndromes without persistent ST segment elevation [5]. Non ST elevation myocardial infarction was excluded through normal values of troponine T (TnT) measured using the Roche COBAS 6000 analyzer system in the Central Laboratory of Clinical County Emergency Hospital of Brasov.

The obesity was diagnosed according to the World Health Organization chriteria taking into account the body mass index values (BMI) values [28].

The uncontrolled diabetes mellitus was considered from values of the HbA1C >7%.

The study was prospective and observational. All the patients signed the informed consent form, approved by the Transilvania University of Medicine Ethics Committee. The follow-up data were collected by phone calls at 3, 6 and 12 months after the hospital discharge.

The demographic data, medical history and clinical data included: age, gender, height, weight, waist circumference (WC), history of diabetes, hypertension, smoking and previous documented ischemic heart disease.

Waist circumference (WC) was measured using a flexible anthropometric tape with precision of 0.1 cm at the midpoint between the iliac crest and the lower costal arch [1]. We used the cutoffs values of WC according to the NCEP-ATP III (men > 102 cm and women > 88 cm) [23], [27]. The body mass index (BMI) was calculated as the weight (kilograms) divided by the square of height (meters).

The hematological and biochemical parameters including hemogram and plasma levels of fasting glucose, urea, creatinine, uric acid, C-reactive protein, total cholesterol and triglycerides were carried out at admission. The biochemical analyses were performed on the Roche COBAS 6000 analyzer system in the Central Laboratory of Clinical County Emergency Hospital of Brasov.

Patients were evaluated by resting ECG and 2D-TTE at baseline and at the discharge from the hospital.

Resting ECG was performed on Nihon Kohden Cardiofax GEM electrocardiograph, and the 2D-TTE on ALOKA Prosound SSD-4000SV machine.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Rel. 7.0) software. Continuous variables are expressed as the mean standard deviation or as median values and range.

The relationship between a continuous variable and a nominal variable was assessed using the T test for independent variables. The differences between the frequency of a nominal data between two groups was assessed using the chi-square test. The independent prognostic value of a variable was calculates using the Cox regression. A p value <0.05 was considered as statistically significant.

4. Results

After one year follow-up, of 140 patients with unstable angina, 125 patients (89.3%) were survivors (Group 1) and 15 patients (10.7%) died (Group 2). The one year mortality rate was 10.71‰.

The analysis of demographic data showed that the mean age of patients who died was significantly higher then the mean age of survivors (75.3±5.9 vs. 64.4±10.4) ($p<0.001$). In group 1 we had 62 (49.6%) females and 63 (50.4%) males. Death occurred more frequent in male [12 (80%)] than in female patients [(3 (20%)], ($p=0.05$). Age over 75 years was independently associated with a higher probability of death (HR 1.2; $p=0.001$).

The analysis of clinical data revealed that patients with prior documented coronary heart disease had a significantly higher risk of death compared to those without previous documented coronary heart disease [11 (73.3%) versus 4 (26.7%) ($p=0.03$)].

In correlation with previous documented coronary artery disease, the 2D-TTE results showed in the group of the patients who died, statistically significant lower values of LVEF [38.6±8.5% versus 50.2±7% ($p<0.001$)], and increased incidence of global hypokinesia [5 (33.3 %) versus 6 (4.8%) ($p= 0.002$)], and septal akinesia [6 (40%) versus 3 (2.4%) ($p= 0.001$)].

Patients with diabetes mellitus in group 2 had a higher risk of death compared to non-diabetic patients in the same group [11(73.3%) versus 4(26.7%) ($p=0.03$)] and the HbA1c plasma levels were significantly higher in the deceased than in the survivors group [8.3±2.4% versus 6.8±2.6) ($p=0.04$)]. Fasting plasma glucose levels showed no statistically significant differences in patients with diabetes who died compared to those who survived [152±56.1 mg/dL versus 150.5±65.6 mg/dL ($p=0.9$)].

Waist circumference >88 cm was found in 2 females (66.7%) from group 2 and in 29 females (46.8%) from group 1, but the difference did not reach statistical significance ($p=0.6$). Waist circumference >102 cm was found in 2 males (16.7%) from group 2 and in 9 males (14.3%) from group 1, and here also, it did not reach statistical significance ($p=1$).

The body mass index (BMI) was higher in the group of male patients who died (29.1±4.5), when compared to the BMI values in the males survivor group (28.4±4.7 cm), without statistically significant differences between the two groups (p=0.06).

The body mass index (BMI) was higher in the group of female patients who died (32±10.9), when compared to the BMI values in the females survivor group (28.5±5.1 cm), without statistically significant differences between the two groups (p=0.6).

The arterial blood pressure levels at admission in the hospital, the fasting plasma glucose levels, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, C–reactive protein showed no statistically significant differences between the two groups.

It is important to underline that our data showed significantly higher values of plasma creatinine in the group of patients who died compared to the surviving patients [1.3 (1; 1.4) vs. 0.9 (0.8; 1.1) (p<0.001)]. The eGRF values calculated using the Modification in Diet in Renal Disease (MDRD) formula, were significantly lower in the group of patients who died compare to the values in the survivors group, in which the eGRF values were in the normal range [(52.6±19.1 ml/min vs. 75.8±21.9 ml/min) (p<0.001)]. These results are consistent with literature data, showing that renal dysfunction is an important prognostic factor for the evolution with major cardiovascular events [20] in patients with coronary artery disease including those with ACS [14].

5. Discussions

In our study population with unstable angina, the elderly people had an increase risk of mortality at one year after the hospital discharge and age over 75 years was an independent predictor of mortality. The mortality risk associated with old age is already revealed both in the GRACE and C-ACS score where age over 75 years is an important parameter [9]. Our study highlights the independent association between age over 75 years and increased risk of death at the one year in patients with unstable angina.

In patients with ACS the presence of diabetes mellitus is associated with a very well known increased risk of morbidity and mortality [18]. Diabetic patients without previous cardiovascular disease have the same long-term morbidity and mortality as non-diabetic patients with established cardiovascular disease after hospitalization for unstable coronary artery disease [18]. Our data revealed a significantly high risk of mortality in patients with unstable angina, correlated with bad control of diabetes. The levels of HbA1c were significantly higher in diabetic patients who died compared to those who survived, the latter subgroup having normal values of HbA1c. In our study the HbA1c values offset the influence of the fasting glucose values on one year evolution of patients with unstable angina. Recent literature data shows conflicting data regarding the relationship between the evolution with cardiovascular events and the values of HbA1C in patients with ACS. Some studies reported the lack of association between HbA1C plasma values and the short-term cardiovascular outcome in diabetic patients admitted with ACS [4]. Other studies reported a high risk of in-hospital mortality and complications in patients with ACS including patients undergoing coronary revascularization [13], [16], [24]. The meta-analysis on the

relationship between HbA1C plasma levels and the evolution with cardiovascular events in patients with coronary heart disease, found that elevated HbA1c levels represents an independent risk factor for mortality in coronary heart disease patients without diabetes, but not in those with established diabetes [26].

A special relationship was described between obesity and cardiovascular risk of patients with established coronary artery disease. Recent studies emphasize the direct relationship between abdominal obesity and major cardiovascular events including death and myocardial infarction in patients with established coronary artery disease [3], [8], suggesting that abdominal obesity acts as a short-and long-term prognostic factor in patients with established coronary artery disease [6], [7]. There are conflicting data regarding the relationship between mortality risk and obesity in patients with acute coronary syndromes. The incidence of mortality after an acute coronary syndrome is significantly associated with age, gender, STEMI, heart failure (HF), and dyslipidemia but not with obesity [22].

Our study performed on patients with unstable angina showed no relationship between mortality risk and BMI or waist circumference in one year evolution after discharge from the hospital.

The literature data describes a paradox in the correlation between body mass index and hospital mortality in patients with ACS in whom the mortality rate decreases as the body mass index increases [19]. The same type of correlation between obesity and cardiovascular mortality was reported after coronary revascularization in elderly patients with acute myocardial infarction [18]. Recent studies showed that BMI was inversely associated with one year mortality rate in patients with acute myocardial infarction [2] and describe an inverse correlation between increased BMI and coronary calcification as "the calcium paradox" rather than "the obesity paradox" [17].

The data from the Swedish Coronary Angiography and Angioplasty Registry, on 64.436 patients with acute coronary syndromes, support the concept of the "obesity paradox". These Swedish registry data describe the relation between BMI and mortality to be U-shaped, with low risk among overweight or obese patients, and underweight and normal-weight patients having the highest risk [8], [22]. Critical evaluation of the studies describing the "obesity paradox" in patients with ACS suggests that the selection or survival bias and treatment bias are important factors to be recognized, and underline the need for further studies in this area [8], [22].

6. Conclusions

Age over 75 years represents an important risk factor for mortality at one year follow-up in patients with unstable angina.

Patients with prior documented coronary heart disease had a significantly higher risk of death compared to those without prior coronary heart disease.

Global hypokinesia, low LVEF and septal akinesia are associated with significantly high mortality risk in patients with unstable angina, at one year follow-up.

Diabetes mellitus and high HbA1c plasma levels, correlate with significantly higher risk of death in patients with unstable angina.

Serum creatinine and estimated glomerular filtration rate are important prognostic factors in the evolution with

cardiovascular death in patients with coronary heart disease. Chronic kidney disease represents a powerful and important risk factor in patients with unstable angina.

We found no relationship between mortality risk and high BMI or waist circumference above normal values, in patients with unstable angina, and this is consistent with "the obesity paradox" described in the literature.

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