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ORIGINAL

GROWTH HORMONE RESISTANCE IN ACUTE MYOCARDIAL INFARCTION

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Background and aim: Hormonal and immunological aspects of acute myocardial infarction (AMI) are in the past decade in focus of interest of researchers. We investigated concentrations of insulin like growth factor 1 (IGF-1), growth hormone (GH), insulin and markers of insulin resistance as like as inflammatory markers in order to find out their role and relationship in AMI.

Material and methods: A prospective study was performed at University Clinical Center Tuzla from January to October 2010. Study group was consisted of 75 patients with AMI. There were 30 healthy controls. Blood samples were taken within first 24 hours of admission and analyzed for GH, IGF-1 and insulin at the Department of Nuclear Medicine. Glucose, glycolised hemoglobin HbA1c, C-reactive protein (CRP), fibrinogen etc. were analyzed by standard methods at Biochemistry unit.

Results: Median of GH in the study group (0,96) was higher than in controls (0,26); p <0.001. Difference in median's concentrations of IGF-1 between AMI and controls was also significant (123 vs. 132 respectively; p< 0,05) as like as IGF-1/GH ratio (p <0.001). Concentration of insulin was higher in study (9,5) than in control group (7,1), but without statistical significance. Despite this, we found out significant difference between concentrations of glucose, HOMA-IR and HbA1C among groups. Levels of CRP and fibrinogen were significantly higher in AMI. Simple linear correlation analysis showed positive correlation between GH and CRP (R 0,350255, p< 0,005).

Conclusions: GH resistance in AMI (Low IGF-1/GH) is probably result of inflammatory/immunological response and therefore could be prognostic marker.

Key words: growth hormone (GH), insulin like growth factor one (IGF-1), insulin, infarction

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Hormonal and immunological aspects of acute myocardial infarction (AMI) are in the past decade in focus of interest of researchers all over the world. Insulin, insulin like growth factor 1 (IGF-1), growth hormone (GH) and markers of inflammation are dancing toghether in complex fashion and making the story of AMI even more difficult to understand. Whether the growth hormone (GH)/insulin-like growth factor 1(IGF-1) axis exerts cardioprotective effects remains controversial and the underlying mechanism(s) for such actions are unclear [1].

Different studies have found different and conflticing results speaking of afore mentioned hormones [2-4]. Therefore, we investigated concentrations of IGF-1, GH, insulin and markers of insulin resistance as like as markers of inflammation in order to find out their role and relationship in AMI and their potential influence at outcome and prognosis of AMI.

Examinees: A prospective clinical study was performed at the Department of Cardiology, Department of Intensive Care with the Coronary care unit and the Department of Cardiovascular Diseases University Clinical Center Tuzla in the period from January to October 2010. There were study and control group as a consecutive sample of 105 patients. Study group was consisted of 75 patients with a diagnosis of AMI (which was analyzed also for the type and localization of AMI). Two patients were excluded from the study due to exclusion criteria, so the analysis was performed on 73 patients with AMI. Diagnosis of myocardial infarction was made following these criteria: anamnesis of chest pain and/or ECG changes suggestive of infarction or ischemia accompanied by an increase of one or more cardiac enzymes to at least twice the upper limit of the normal value at the laboratory of our hospital. Baseline characteristic of patients involved in our study are given in table 1.

The study was approved by the local ethics committee, and all patients gave written informed consent to participate.

Table 1. Baseline characteristic of patients

Age	58,6 ± 11,7
Male/Female	51/22 (69,9% / 30,1%)
STEMI/NSTEMI	43/30 (58,9% / 41,1%)
Fibrinolytic therapy	35 (47, 9%)
Anterior vs. inferior wall infarction	31/42 (42,5% / 47,5%)
Number of diseased coronary vessels	
3-vessel disease	25 (34,2%)
2-vessel disease	23 (31,6%)
1-vessel disease	24 (32.8%)
Left Main stenosis (LMT)	1 (1,4%)
Hypertension	30 (41.1%)
Previosly diagnosed diabetes	15 (20,5%)
Dyslipidemia	38 (52,1%)
CHOL	5,85 ± 1,16
LDL	3,84 ± 1,12
HDL	0,92 ± 0,31
TGL	2,67± 1,72
Smokers	28 (38,4%)

Data are shown as mean ± SD or number of patients (%). STEMI ST elevation myocardial infarction, NSTEMI non ST elevation myocardial infarction, CHOL cholesterol, LDL low density lipoprotein, HDL high density lipoprotein, TGL triglicerids

Methods: Blood samples were taken and analyzed for next hormones: growth hormone, IGF-1 and basal insulin at the Department of Nuclear Medicine, Tuzla. Fasting concentrations of these hormones were taken from blood samples in first 24 hours of admission, in the morning, in Intensive Care Unit and were measured after freezing at -20□C, centrifugation and aliquation at Department for Nuclear medicine in Tuzla. Growth hormone was measured with IRMA125 Sandwich Immunoradiometric Assay – IRMA) (DiaSorin, Stillwater, USA), using automatic gamma counter for gamma emiters. IGF-1 was measured with RIA (eng. Radioimmunoassay-RIA) (DiaSorin, Stillwater, USA) method using 1470 Automatic Gamma Counter (Wallac Wizard). Basal insulin was measured using IRI125 (eng. Immuno-Radioactive-Insulin - IRI) (DiaSorin, Stillwater, USA) with Automatic Gamma Counter (Wallac Wizard).

A haemogram, enzymes of myocardial necrosis (troponin I, creatine kinase, creatine kinase myocardial fraction), electrolyte concentrations, glucose, urea, creatinine, uric acid, lipid profile and all other biochemistry measurements were carried out by the analytical unit of the Biochemistry Department of our institution by standard methods.

Echocardiography: Ejection fraction (EF) was determined using Simpson's method (rule) on two dimensional Vivid 3 ultrasound. Localization of AMI was also determined by ultrasound oh heart (echocardiographicaly).

Statistical methods: SPSS V.15 software (SPSS Inc, Chicago, Illinois, USA), Arcus Quick Stat and Microsoft Excel XP Professional were used for statistical analysis of the study. Variables with asymmetric distribution were summarized as medians and interquartile ranges. Normality tests (Shapiro-Wilk) were used for all variables. In the comparison between patients with AMI and controls, continuous variables that were normally distributed were analyzed with the two-tailed t test and unequally distributed variables were analyzed with the Mann–Whitney U test. Categorical data and proportions were analyzed with the $X2$ or Fisher's exact test where appropriate. The ratios of IGF-1 to GH concentrations were calculated by dividing IGF-1 concentrations by GH concentrations and these ratios were compared between the two groups. Analysis of regression and correlation were used, too. A value of two-sided P< 0,05 was considered significant.

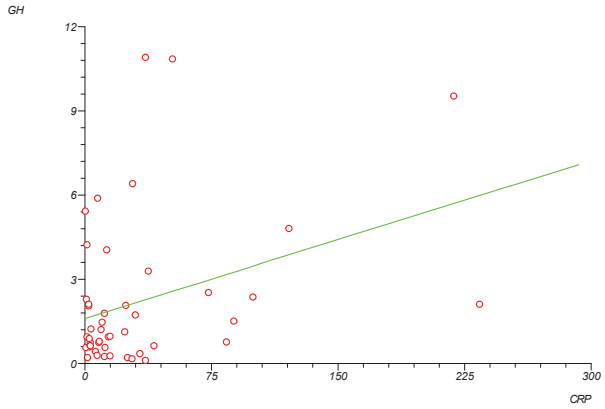
Results: Median of growth hormone in the study group was higher than in controls with very significant difference (p <0.001). Shapiro Wilk test showed that variables were not normally distributed, so Mann-Whitney test was performed for analyses of all parameters that we evaluated. Difference between concentrations of IGF-1 in study and control group is also statistically significant with p< 0,05. The ratio (quotient) IGF-1/STH was also significantly lower in the study group (p <0.001). Concentration of basal insulin was higher in study than in control group, but without statistical significance, even tough there were tendency for statistical significance.Despite this, we found out significant difference in concentrations of glucose, HOMA-IR and HbA1C between these two groups. Levels of nonspecific markers of inflammation (CRP, fibrinogen) were also significantly higher in patients with AMI. Median values with values of lower and upper quartile, as like as p

Table 2. Concentrations of examinated parametars in study and control group

	Study group	Control group	p value
IGF-1	123 (82-159)	132 (125-166)	< 0,05
GH	0,96 (0,6-2,4)	0,26 (0,1-0,7)	< 0,001
IGF1/GH	89 (39-245)	507 (118-1100)	< 0,001
insulin	9,5 (6,3-18)	7,1 (4,9-12,6)	0,07 (n.s)
glucose	7,5 (5,8-10)	5,2 (4,8-5,5)	< 0,001
HOMA -IR	4,16 (1,5-8,6)	1,76 (1,2-2,4)	< 0,001
HbA1c	5,9 (5,5-7,6)	5,5 (5,2-5,7)	< 0,05
CRP	11,8 (3,4-34)	1,65 (1,1-2,4)	< 0,001
fibrinogen	4,03 (2,9-6,3)	3,15 (2,9-3,9)	< 0,05

values, are shown in Table 2. Simple linear correlation analysis showed the existence of a positive linear correlation between GH and CRP (R 0,350255, p< 0,005) and this is shown in Figure 1.

Values are presented as medians with values of lower and upper quartiles in brackets respecitevely followed by p-value according to Mann-Whitney analysis. STEMI – ST elevation myocardial infarction, NSTEMI- non ST elevation myocardial infarction, IGF-1 insulin like growth factor 1, GH- growth hormone, HOMA-IR index of insulin resistance, HbA1c – glicolised haemoglobin, CRP -C reactive protein.



(r) = 0,350255, p = 0,0158

Figure 1. Simple linear correlation between GH and CRP

DISCUSSION

First of all, we investigated metabolic status of patients with AMI. We expected to find higher degree of insulin resistance in AMI group than in control group, and we proved our hypothesis using HOMA-IR index of insulin resistance. Levels of glucose concentration and HbA1c were also significantly higher in AMI group and these results are similar to results of few other recent studies [2; 4-9]. Basal insulin levels showed no significant difference between groups and this is also concordant to few other investigations. In afore mentioned investigations authors found insulin resistance without significant increase of basal insulin [2, 6].

Few previous studies reported that IGF-1 is decreased in AMI [2, 3, and 4]. However, the role and relationship of IGF-1/GH/ insulin remains unclear [1-4] and this was in the focus of interest of our investigation. As we mentioned above, the level of IGF-1 is lower in patients with AMI than in controls, and the difference between these two groups in our study is statistically significant (P<0, 05).

Growth hormone concentration is higher in patients with AMI than in controls in our study (p< 0,001). Higher levels of GH and lower levels of IGF-1 are suggestive for growth hormone resistance. Growth hormone resistance is well described in patients with chronic heart failure (CHF), but it is interesting that we found high levels of GH and low levels of IGF-1 in an acute condition – AMI. What is the underlying mechanism for GH resistance in AMI?

The acute changes in the growth hormone concentration appeared to be linked to the degree of the inflammatory reaction and stress provoked by the infarction. We found strong positive linear correlation between CRP and GH and similar result have found couple of Swedish authors in their study [4]. In the other words, the higher the levels of C-reactive protein, the higher were the levels of growth hormone. It's well known that inflammation plays important role in pathogenesis and course of acute coronary syndrome. Previous studies have found that concentration of CRP is elevated in first 24 hours of AMI [10-14]. We found not just significantly elevated level of CRP in group of patients with AMI but also elevated level of fibrinogen in AMI, which is similar to results of another study [15]. However, in this investigation we haven't found only elevated levels of nonspecific markers of inflammation but also strong positive correlation between inflammation and IGF-1/GH axis. Hereby we need to mention that there was nor linear correlation between IGF-1 and markers of inflammation neither linear correlation between GH / IGF-1 and markers of insulin resistance (glucose, insulin, HbA1c, HOMA-IR). This emphasis once more the significance of correlation (relationship) between GH and inflammatory/immunological response. Afore mentioned correlation might be reason for conflicting results of GH concentrations in acute myocardial infarction. Friberg et al. (2000) have found similar results as we did in their study, but on contrary Conti et .al. (2001) found decreased level of GH in AMI. We hy-

pothesize that in extensive myocardial infarction with strong immunological/inflammatory response GH is secondarily rising. In less extensive infarctions with mild inflammatory response and better course and prognosis GH is not rising and it remains at the same level as it was before AMI. This could be explanation for different and conflicting findings of GH levels in AMI. GH resistance might be marker of course and prognosis of AMI. The lower IGF1/GH ratio the poorer course and prognosis of AMI. However, further investigations need to be done to confirm this hypothesis.

Conclusions: As we've pointed out, the main findings of our research are lower IGF-1 and higher GH values in AMI than in control group. In the other words we found out low IGF-1/GH ratio in AMI (so called growth hormone resistance) and elevated levels of markers of inflammation and insulin resistance. Strong linear positive correlation between CRP and GH is probably the key of GH resistance state. IGF-1/GH ratio could be good marker of myocardial outcome and prognosis, but further investigations need to be done to confirm this.

Conflict of interests: none

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