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Research Article/Araştırma Makalesi

Is IGF-1 level actually lowered in the early stage following an acute myocardial infarction and is IGF-1 associated with the left ventricle dysfunction or cardiac events?

Serum IGF-1 düzeyleri akut miyokard infarktüsü sonrası gerçekten azalır mı ve sol ventrikül disfonksiyonu ile ilişkili midir?

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ABSTRACT

Background: Insulin-like growth factor (IGF) is the primary mediator of growth hormone. IGF-1 may have an important role in protecting the myocardial functions following an acute myocardial infarction (AMI). Literature reveals only a limited number of studies investigating the relationship between the serum IGF-1/IGF binding protein-3 (IGFBP-3) levels and the left ventricular functions post AMI. We aimed to determine IGF-1 and IGFBP-3 levels and evaluate their effect on cardiac functions post AMI.

Material and Method: Sixty five patients who were included in the study and the control group had 26 patients. Blood samples of the patients were obtained on the second day of their admission. The patients underwent echocardiographic examination on the 7th day of their hospitalization.

Results: The serum IGF-1 and IGFBP-3 levels of the patient group were higher than those of the control group; however only IGF-1 levels were statistically significant (243,2±87,9 ng/mL versus 177,2±81,8 ng/mL p=0,001). The increase in the wall thickness and LV chamber size did not correlate with the decrease in LVEF and IGF-1/IGFBP-3 levels. The patients who had minor cardiac events had lower IGF-1 levels but this was not statistically significant (210.5±88.5 versus 253.1±86.1 p>0.05).

Conclusion: IGF-1 and IGFBP-3 levels elevated following an the early AMI, but these markers were not correlated with the echocardiographical measurements in early post MI period.

Keywords: Insulin-like growth factor, insulin-like growth factor binding proteins, acute myocardial infarction

ÖZ

Amaç: İnsülin benzeri büyüme faktörü (IGF), büyüme hormonunun primer mediatörüdür. IGF-1, akut miyokard infarktüsünü (AMİ) takiben miyokard fonksiyonlarını korumada önemli bir rol oynayabilir. Literatürde, serum IGF-1/IGF bağlayıcı protein-3 (IGFBP-3) seviyeleri ile AMI sonrası sol ventrikül fonksiyonları arasındaki ilişkiyi araştıran sınırlı sayıda çalışma vardır. AMİ sonrası IGF-1 ve IGFBP-3 seviyelerini belirlemekyi ve AMİ sonrası kalp fonksiyonlarına etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya dahil edilen 60 hasta ve kontrol grubunda 26 hasta vardı. Hastaların kan örnekleri başvurularının ikinci gününde alındı. Hastalar hastaneye yatışlarının 7. günü ekokardiyografik olarak değerlendirildi.

Bulgular: Hasta grubunun serum IGF-1 ve IGFBP-3 düzeyleri kontrol grubundan daha yüksekti; ancak sadece IGF-1 seviyeleri istatistiksel olarak anlamlıydı (243,2±87,9 ng/mL, 177,2±81,8 ng/mL, p=0,001). Duvar kalınlığı ve LV boşluk boyutlarındaki artış, LVEF ve IGF-1/IGFBP-3 seviyelerindeki azalma ile ilişkili değildi. Minör kardiyak olayları olan hastalar düşük IGF-1 seviyelerine sahipti, ancak bu istatistiksel olarak anlamlı değildi (210,5±88,5 ve 253,1±86,1 p>0.05).

Sonuç: IGF-1 ve IGFBP-3 seviyeleri, AMİ sonrası erken dönemde yükselmiştir, ancak bu belirteçler, Mİ sonrası erken dönemde ekokardiyografik ölçümlerle korele değildi.

Anahtar Kelimeler: İnsülin benzeri büyüme faktörü, insülin benzeri büyüme faktörü bağlayıcı proteinler, akut miyokard infarktüsü

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INTRODUCTION

The insulin-like growth factor (IGF) is the primary mediator of the growth hormone. The effects of IGF are reflected via autocrine, paracrine, and endocrine routes and its regulation involves complex mechanisms. IGF-1 is transported in the blood circulation by carrier proteins that are known as IGF binding proteins (IGFBPs) (1-5). IGF-1 has a key role in the proliferation, modification of cells in many tissues, including the myocardium, as well as in inhibition of cell necrosis and apoptosis. Several studies were performed on coronary diseases and IGF relation (Several studies were performed on coronary diseases and their relationship with the IGF). Although the results were controversial, IGF-1 may have an important role in protecting the myocardial functions following an acute myocardial infarction (AMI) (5-7). However, there is an only a limited number of studies, which were performed with a small number of patients to investigate the relationship between the serum IGF-1/IGFBP-3 levels and the left ventricular functions post AMI, and it remains uncertain whether the IGF or IGFBPs is the marker of ventricular dysfunction. We, therefore, aimed to investigate the levels of serum IGF-1 and IGFBP-3 and determine their effect on cardiac functions following an early post AMI period.

MATERIAL AND METHOD

A total of 65 patients, who were diagnosed with AMI, admitted to our coronary care unit (mean age: 52±9 years; 59 males, 6 females) and were included in this study. The control group consisted of 26 strictly speaking healthy subjects (mean age: 51±8 years; ranging between 40 and 73 years old; 21 males, 5 females) with no coronary artery diseases and exclusion criteria provided below. The diagnosis of AMI was established according to World Health Organization criteria (8). Patients with uncontrolled hypertension (systolic blood pressure (SBP) being 140 and/or diastolic blood pressure (DBP) being 90 mmHg or higher based on their history), diabetes mellitus, acromegaly, history of coronary artery disease or heart failure, thyroid disease, hepatic dysfunction, Killip score of 3-4, aorta or mitral valve dysfunctions, cardiomyopathy, history of acute pericarditis or myocarditis, left branch block or atrial fibrillation on the electrocardiography, acute or chronic renal failure, systemic infections, musculoskeletal diseases, malignancy, and those who were on a medication that would affect IGF-1/IGFBP-3 serum levels were excluded from the study.

Patients were treated according to the American College of Cardiology/American Heart Association guidelines. Aldosterone antagonists were not initiated for any of the patients. All patients underwent coronary angiography, which demonstrated that 32 had a percutaneous coronary intervention.

Study protocol: Fasting blood samples of the patients were obtained on the second day of their admission between 08:00 am and 09:00 am to determine C-reactive protein (CRP), IGF–1 and IGFBP–3 levels (the first morning after the admission was considered the first day). In the first 24 hours, a series of measurements for creatine kinase (CK)/CK-MB were performed. In the control group, fasting blood samples were obtained on the same day between 08:00 am and 09:00 am, and IGF-1, IGFBP-3, fasting blood glucose (FBG), hemoglobin A1c (HgA1c) levels, and thyroid hormones levels were measured. The weight and height of the participants included in the study were recorded and their body mass indexes (BMI) were calculated.

Laboratory Studies: Insulin-like growth factor-1 and IGFBP-3 levels were measured by immunoradiodynamic measurement method (IRMA) randomly in controls and patients sera separated from the blood. DSL-5600 ACTIVE® IGF-1 with EXTRACTION (Diagnostic system laboratories, Inc®, Texas, USA) for IGF-1 levels, and DSL-6600 ACTIVE® IGFBP-3 (Diagnostic system laboratories, Inc®, Texas, USA) for IGFBP-3 level kits were used. High sensitivity C-reactive protein (hsCRP) levels were measured with the Hs-CRP BN2 model nephelometer (Dade-Behring®).

Echocardiography Measurements: The patients underwent a conventional echocardiographic examination on the 7th day of their hospitalization using Vingmed System 5 (General Electronic Horten, Norway) echocardiography device.

In accordance with the standards defined by American Echocardiography Association, the left ventricular diastolic (LVIDd) and systolic (LVIDs) diameters, interventricular septum (IVSWT) and posterior wall (LVPWT) diastolic thicknesses were measured on the parasternal long axis by M mode echocardiography. On the apical 4-chamber view, LV ejection fraction (LVEF) and LV end systolic (LVVs) and end diastolic (LVVd) volumes were measured by Simpson's method. Fractional shortening (FS) was calculated with (LVIDd-LVIDs)/LVIDdX100 formula. Cardiac output (CO) was calculated with LVVd-LVVs/1000 X heart rate. The left ventricular mass was calculated using the Devereux formula. LV mass (gr) = 1.05 X 0.8 X((LVPWT + IVSWT + LVIDd)^3-(LVIDs)^3)+0.6 (9).

In Hospital Cardiac Events: Death, re-infarction, stroke, revascularization, ischemia, arrhythmia and heart failure were defined as cardiac events during hospitalization.

Statistical Analysis: The analyses were performed using SPSS V 16.0 for Windows (version 16.0, SPSS, Chicago, Illinois, USA). Quantitative variables were expressed as mean ± SD for parametric variables, and median and minimum-maximum levels for non-parametric variables. Comparison of parametric data between the two groups was performed by means of the Independent-Samples T test. A comparison of non-parametric data between the two groups was performed by the Mann –Whitney U test. Categorical variables were compared by the chi-squared test. Pearson's test was used to correlate the parametric variables, and Spearman's test was used for non-parametric variables. Two-tailed p-value <0.05 was considered statistically significant. Receiver operating characteristics (ROC) analysis was performed. The optimum cut-off value was determined and the sensitivity and specificity were reported at that point.

Patients were divided into two groups according to the ROC curve analysis of IGF1 (low IGF-1 levels group, high IGF-1 levels group).

Ethical Declaration: All patients were informed that the study protocol was approved by the local ethics committee.

RESULTS

The main characteristics of the patients and the controls were presented in **Table 1**.

Table 1. Comparison of the baseline characteristics of the subjects

	Patient Group n:65	Control Group n:26	p
Age, year	52±9	51±8	NS
Gender, male	59 (90.8%)	21 (80.8%)	NS
BMI, kg/m^2	27±4	28±3	NS
Heart Beat/min	71.09±10.01	72.42±6.92	NS
SBP, mmHg	103.6±13.9	109.2±10.5	<0.05
DBP, mmHg	55.7±10.0	57.9±9.2	NS
FBG, mg/dl	64.1±18.8	68.8±14.5	NS
HgA1c, mg/dl	5.6±0.4	5.5±0.3	NS
HDL, mg/dl	46.8 ±10.6	46.2±11.1	NS
LDL, mg/dl	113.2±29.9	108.5±38.1	NS
TC, mg/dl	189.2±33.4	185.4±37.8	NS
TG, mg/dl	145.6±119.2	153.2±75.8	NS
Creatinine,mg/dl	0,99±0,2	0,93±0,1	NS
Albumin, mg/dl	3,6±0,7	3,4±0,2	NS

Abbreviations: BMI: body mass index, DBP: diastolic blood pressure FBG: fasting blood glucose, HDL: high density lipoprotein, LDL: low density lipoprotein, NS: not significant p<0.05: Statistically significant, SBP: systolic blood pressure TC: total cholesterol, TG: triglyceride.

All the characteristics, except SBP, were similar in both of the groups. The serum IGF-1 and IGFBP-3 levels of the patient group were higher than those of the control group; however, only IGF-1 levels reached a statistically significant level (**Table 2**). The only significant correlation was between the IGF-1 levels and the age (r=-0.380, p=0.02).

Table 2. Comparison of serum IGF-1/IGFBP-3 levels after acute myocardial infarction

	Patient Group	Control Group	p
IGF-1, ngr/ml	243,2±87,9	177,2±81,8	0,001
IGFBP-3, ngr/ml	3296,7±859,3	2860,8±1077,0	0,100

Abbreviations: IGF-1: insulin-like growth factor-1, IGFBP-3: IGF binding protein-3

The relationship between the serum IGF-1/IGFBP-3 levels on the second day and the conventional echocardiographic parameters prior to discharge was evaluated. The increase in the wall thickness and LV chamber size and the decrease in LVEF and IGF-1/IGFBP-3 levels were not correlated. There was no difference between the echocardiographic parameters of the patients with low or high IGF-1and the IGFBP-3 levels (**Table 3**). Similarly, there was no difference in the IGF-1 levels when the patients were categorized by LVEF into two groups, ones with LVEF being lower than 55% and the other with LVEF being greater than 55%.

Table 3. Comparition of laboratory and epidemiologic parameters between patients with high and low levels of IGF-1

	Low IGF-1	High IGF-1	p
Age, years	57 ± 8	50 ± 9	0.03
HgA1c, mg/dl	5.7±0.4	5.6±0.5	0.5
FBG, mg/dl	61 ± 23	65 ± 16	0.7
Peak CK-MB, IU/L	248 (53-770)	282 (28-621)	0.9
TC, mg/dl	180± 30	193±34	0.1
TG, (mg/dl	101(53-217)	116(48-833)	0.3
HDL, mg/dl	46±12	47±9	0.8
LDL, mg/dl	110 ± 32	114 ± 29	0.6
CRP, mg/L	23 (5.7-136)	38.9 (3-200)	0.5
LVIDd, mm	51±0.5	52±0.6	0.6
LVIDs, mm	34±0.5	37±0.7	0.9
LVVd, ml	93±32	94±27	0.9
LVVs, ml	43±20	42±15	0.6
LVPWDT	1±0.1	1±0.2	0.4
IVSDDK	1±0.2	1.1±0.2	0.9
EF, simpson, %	54 ± 9	56 ± 8	0.4
CO, ml/dak	3,5 ± 1	3,7 ± 1	0.3
LV mass, gr	217 ± 65	227 ± 77	0.9

Abbreviations: CK-MB: creatine kinase , CO: cardiac output, CRP: c reactive protein, MB, EF: ejection fraction, FBG: fasting blood glucose, HDL: high density lipoprotein, IVSWT: interventricular septum diastolic thicknesses, LDL: low density lipoprotein, LV: left ventricule, LVIDd: left ventricle diastole diameter, LVIDs: left ventricle systole diameter, IVSWT: interventricular septum diastolic thicknesses, LVPWT; posterior wall diastolic thicknesses, TC: total cholesterol, TG: triglyceride

IGF-1 and in-hospital events: None of the patients experienced death, re-infarction, stroke, and revascularization. However, 15 patients (23%) had other cardiac events (ischemia (n=11), arrhythmia (n=2) and heart failure (n=2)). Although the IGF-1 and IGFBP-3 levels of the patients with in-hospital events were slightly lower, the difference was not statistically significant (**Table 4**).

Table 4. Cardiac events during hospitalization and IGF-1/IGFBP-3

	Event (n=15)	No events (n=50)	P
IGF-1,ngr/ml	210.5±88.5	253.1±86.1	NS
IGFBP-3, ngr/ml	3143.3±559.3	3411.3±900	NS

Abbreviations:IGF-1: insulin-like growth factor-1, IGFBP-3: IGF binding protein-3

The predictive value of serum IGF level for AMI, (sensitivity of 72.3% and specificity of 61.5%, area under the ROC curve = 0.716) was 198.2 ngr/ml (**Figure 1**). The predictive value of serum IGFBP level for AMI, (sensitivity of 67.7% and specificity of 57.7%, area under the ROC curve = 0.612) was 2826ngr/dl (**Figure 2**).

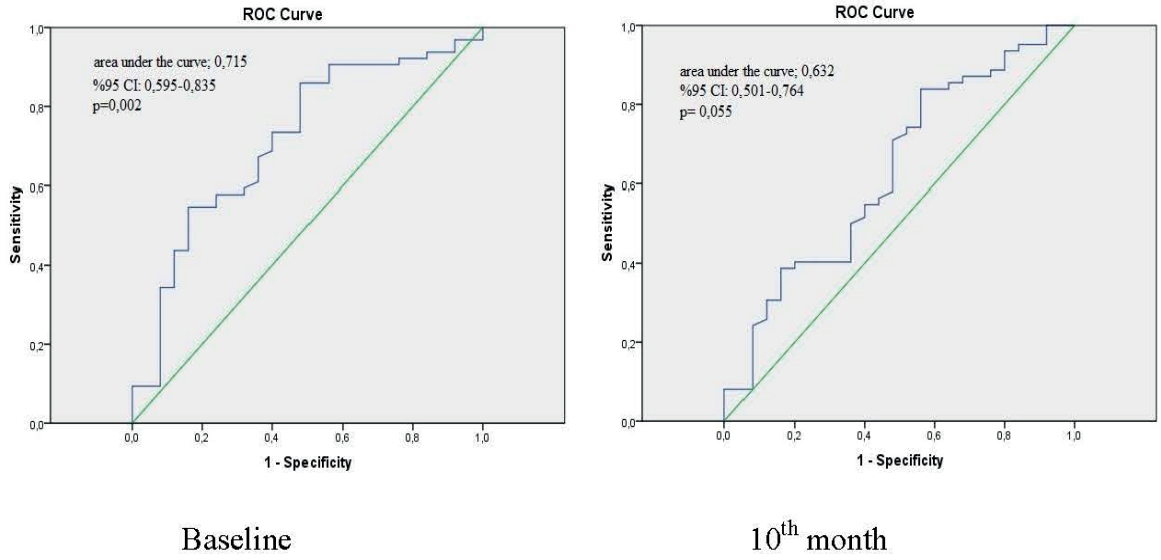

Figure 1: The receiver operating characteristic (ROC) curve of IGF-1 at baseline and the 10th month

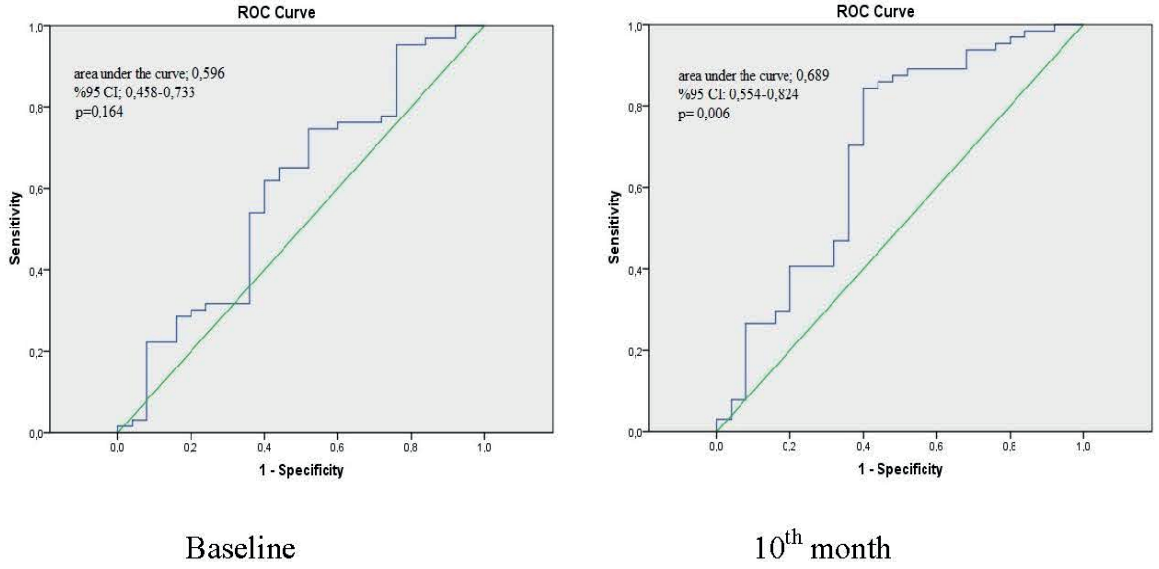

Figure 2: The receiver operating characteristic (ROC) curve of IGFBP-3 at baseline and the 10th month

DISCUSSION

In the present study, we found that IGF-1 and IGFBP-3 levels elevated following an early AMI, but these markers were not correlated with the echocardiographical measurements in the early post MI period.

A number of epidemiological studies investigated the association between the IGF/IGFBPs and CAD. Mainly, the low IGF-1 and high IGFBP-3 levels were associated with CAD (7,10,11). On the other hand, the results from a few studies that examined the association between the IGF-1/IGFBP-3 levels and the early post AMI period were controversial. In almost all studies, levels of IGF-1 were lower or did not change in the setting of AMI (12-15). For example, Friberg et al. (13) investigated the serum IGF-1 levels on a small number of AMI patients. They reported low serum IGF-1 levels. However, their patients were not homogenous because the patients with a history of previous diabetes mellitus, CAD and heart failure were included in the study. Yamaguchi et al. (14) reported a low concentration of serum IGF-1 on the admission of AMI. Unfortunately, a control group was not used, and obese and diabetic elderly patients with heart failure were included in this study. Similarly, Hajsadeghi et al. (15) showed that IGF-1 levels in the first 24 hours following AMI were found to be lower in the comparison with the control group.

To our knowledge, there is only one study demonstrating the increased IGF levels in the early post AMI period (16). Lee et al. (16) reported that only levels of free IGF-1 were higher than those of the control group, but the levels of total IGF-1 were not increased. In our study, the serum total IGF-1 levels were significantly higher than those of the control group. Our study is the first to show increased levels of IGF-1 in the AMI. We consider that there are some reasons which might be responsible for our different results: first, the number of patients was greater in

our study than the previous studies. Secondly, our patients were relatively younger than those in the previous studies we have provided above. For instance, our patients' mean age was 59 whereas the patients' mean age of the Friberg's study was 69 (13). So, we conclude that the age and IGF-1 levels were negatively correlated. In addition, our study group was homogenous and we did not include any disorders, which could affect the IGF-1 levels, such as diabetes, CAD, and heart failure.

The studies indicating the beneficial effects of IGF-1 in AMI have suggested different underlying mechanisms. IGF-1 increases the glucose flow into the cells (17-18), stops apoptosis in the smooth muscle cells (19-21) and increases the proliferation and migration of the smooth muscle cells, thereby increasing plaque stabilization (3). It also increases nitric oxide production in the endothelium and vascular smooth muscle cells (2) and reduces the reperfusion injury and cardiomyocyte loss post AMI (22). Also, it facilitates neovascularization by increasing the endothelial growth factor (23-24).

It is known that the low levels of IGF-1 are associated with the risk of developing heart failure. Further studies have accentuated the stimulating effect of IGF-1 on ventricular remodeling and long term survival following myocardial infarction. In the literature, there is an only a limited number of studies investigating the relationship between the serum IGF-1/IGFBP-3 levels and the left ventricular functions post AMI. Lee et al. (16) investigated 34 MI patients and 17 controls to determine the relationship between IGF-1 levels and some LV measurements. They found a negative correlation between the 2.nd, 3.th and 7.th day IGF-1 levels and LV mass, LV end systolic-end diastolic diameters. In addition, they reported a positive correlation between the total IGF-1 levels and LVEF, however, no correlation was found with the free IGF-1. Another major outcome of this study was that myocardial remodeling and ventricular function were favorable in patients with IGF-1 level being higher at the onset of MI. However, Friberg et al. (13) did not found a correlation between IGF-1 and LVEF or cardiac output. In our study, no correlation was found between the changes in the left ventricle systolic function and IGF-1 levels. This finding might be due to several reasons such as the lower rate of myocardial necrosis, good general performance index and high levels of baseline EF in our patient group which might have affected the evaluation of the benefits offered by IGF-1. Furthermore, ACEIs and B-blockers were not withdrawn. Their use might have reduced the LV systolic dysfunction, unmasking the effects of IGF-1. Furthermore, the serum IGF-1/IGFBP-3 levels may not reflect the tissue level and IGF-1/IGFBP-3 might also have autocrine or paracrine effects. These results suggest that IGF-1 may not be a reliable predictor of cardiac changes observed post AMI in patients with limited necrosis and better general performance.

Yamaguchi et al. (14) reported that a low concentration of serum IGF-1 on admission was associated with a poor early prognosis of AMI. However, these lowered IGF-1 levels were normalized in three months of AMI. Lee et al. (16) found that patients who had poor prognosis had significantly lower IGF-1 levels than good survival. They demonstrated that IGF-1 levels were lowered by the 7.th day of MI then IGF-1 levels were returned the previous levels. Hajsadeghi et al. (15) indicated that IGF-1 levels in the first 24 hours following AMI were found to be lower in comparison with the control group, and the serum total IGF-1 concentration did not seem to be associated with short-term survival (15). The evaluation of in-hospital events (arrhythmia, ischemia, and heart failure) revealed that the patients, who developed complications, had lower levels of IGF-1 and IGFBP-3; however, the differences were not statistically significant (p=0,1). In earlier studies, low IGF-1 levels and major cardiac events were found to be associated (13-17,25). In our study, no major cardiac events were observed; thus, their relationship with the IGF-1 level could not be evaluated. This positive result may be due to the higher IGF-1 levels of our patients at the beginning of the AMI. The increased possibility that during the first few days of AMI, the total IGF-I level may be used to predict the patient's prognosis.

There are 6 types of IGF carrier proteins known in blood circulation. IGFBP-3 is the most common form in serum (96%). The biological effects of IGF-1 can be increased or decreased by IGFBPs (16,26,27). In our study, the serum IGFBP-3 level was high but did not reach a statistically significant level, which is consistent with the findings in the literature.

According to the correlation analysis, IGF-1 and age were negatively correlated, which is again consistent with the findings in the literature (r=-0.291, p=0.001). Serum CK/CKMB and CRP levels were not correlated with IGF1 and IGFBP 3. These findings suggest that IGF-1 is not correlated with the severity of necrosis and that it is not expressed as an acute phase reactant.

The main limitations of this study are: 1. Although our patient number is higher than the previous studies, our patient and control number is small. 2. We examined only total IGF-1 and IGFBP-3 levels, but free IGF-1 levels and IGFBP-1 levels did not examine. 3. The seventh day after AMI may be early for evaluation of cardiac function.

CONCLUSION

Serum IGF-1 levels were significantly higher in patients with AMI than those of controls; however, it was not related to in-hospital cardiac events and echocardiographic parameters of the patients. We consider that the relationship between the AMI and IGF/IGFBPs is complex and further studies are required to explain this association.

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