The correlation of plasma adiponectin level and infarct size in ST elevation myocardial infarction measured by cardiac magnetic resonance image

Chan Joo Lee

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Donghoon Choi

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Chan Joo Lee

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This certifies that the Master's Thesis of
Chan Joo Lee is approved.

_____
Thesis Supervisor : Donghoon Choi

_____
Thesis Committee Member : Jeong-Ho Kim

_____
Thesis Committee Member : Jung-Sun Kim

The Graduate School
Yonsei University

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<ABSTRACT>

The correlation of plasma adiponectin level and infarct size in ST elevation myocardial infarction measured by cardiac magnetic resonance image

Chan Joo Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Donghoon Choi)

Background : Currently, adiponectin is regarded as predicting the risk and prognosis of coronary artery disease. However, it is still unclear whether the level of plasma adiponectin could be useful biomarker for myocardial infarction or not. To demonstrate the controversial factor, the association between adiopnectin after acute myocardial infarction (AMI) and myocardial infarct size measured by cardiac magnetic resonance image (CMRI) were analyzed in this study.

Methods : Plasma concentration of adiponectin was measured in 31 patients who underwent successful primary coronary revascularization after acute myocardial infarction (AMI). Blood samples were obtained immediately after admission and at 6, 24, 48, and 72 hours after revascularization. Total LV mass, infarct mass, and microvascular obstruction (MVO) were measured by CMRI and relative infarct mass, relative MVO were calculated. Left ventricular ejection fraction (LVEF) was assessed

by echocardiography.

Results : After AMI, plasma adiponectin levels did not significantly change compared with the initial level. Plasma concentrations of adiponectin immediately after AMI correlated positively with HDL-cholesterol ($r = 0.45$, $p < 0.05$) and negatively with triglyceride ($r = -0.41$, $p < 0.05$). During 72 hours after admission, none of the plasma adiponectin levels correlated with a relative infarct mass, relative MVO, or left ventricular ejection fraction.

Conclusion : Plasma adiponectin levels during the early phase of myocardial infarction did not correlated with infarct size. Therefore, adiponectin might be not u seful as a biomarker for estimating of myocardial damage and systolic function.

Key Words : adiponectin, myocardial infarction, cardiac magnetic resonance image

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I. INTRODUCTION

Adioponectin is a collagen-like protein derived from adipocyte.[1] Concentrations of serum adiponectin are decreased in patients with obesity, non-insulin dependent diabetes mellitus (NIDDM), and coronary artery disease.[2] Experimental studies showed that the roles of adiponectin suppress the progression of atherosclerosis, chronic vascular insufficiency, and hypertension.[3-6] Low plasma concentration of adiponectin could predict the development of cardiovascular disease, consequently.[7]

Recent studies showed that circulating concentration of adiponectin directly after acute myocardial infarction (AMI) might be a predictive factor for prognosis of the disease.[8] Shibata *et al.* studied that the correlation of adiponectin with initial perfusion defect size, final infarct size at 6 months after AMI, and the extent of recovery were

evaluated by single-photon emission computed tomographic (SPECT) images. They showed that final infarct size were associated negatively with plasma adiponectin levels after AMI. The results suggested adiponectin levels after coronary intervention were a good indicator of recovery from cardiac injury after reperfusion treatment for AMI.[9]

Yet there is conflicting information about the level of plasma adiponectin immediately after AMI. Little is known about the association between adiponectin levels and the extent of myocardial damage. In this study, we investigated the variation of plasma adiponectin level during the acute phase of ST-segment elevated AMI. We also examined the correlation of serial plasma adiponectin level and infarct size as measured by a novel cardiac imaging tool, cardiac magnetic resonance image (CMRI) analysis.

II. MATERIALS AND METHODS

1. Subject

A total of 31 patients with ST-segment elevated AMI treated successfully by primary percutaneous coronary intervention were enrolled in this study. All the patients underwent CMRI and echocardiogram. For the examination of infarct size, CMRI was taken 7 days after the primary percutaneous coronary intertvention (PCI). Patients with recurrent chest pain associated with ST-segment changes during the time between

primary PCI and CMRI were excluded. AMI was defined as patients presenting within 12 hours of onset of chest pain, with 2 mm ST elevation in 2 continuous leads on the presenting electrocardiogram and angiography occlusion of a coronary artery.

2. Blood sampling

In the patient with AMI, blood sampling for adiponectin was performed immediately after admission and at exactly 6, 24, 48, and 72 hours after revascularization. Plasma levels of fasting glucose, HbA1c, lipid profile, and electrolyte were measured at admission. The concentrations of plasma adiponectin were determined by commercially available ELISA kit (R&D systems, Minneapolis, MN, USA).

3. CMRI protocol

A cardiac MRI scan was performed within 7 days after the primary PCI, with a 1.5 Tesla (T) MRI unit (Gyroscan Intera, Philips Medical Systems, Netherlands), which was equipped with a dedicated cardiac software package and a dedicated cardiac phased-array surface coil. Delayed enhancement images were acquired by an inversion-recovery segmented gradient echo T1 weighted sequence 10 min after the intravenous injection of gadolinium-DTPA at a dose of 0.2 mmol/kg body weight. For data acquisition, the following parameter was used: typical TR/TE = 5.3/1.6 ms, flip angle = 15°, slice thickness = 10 mm, field of view = 360 mm, matrix = 512 x 512, and number of signal average = 2. The inversion time was determined by a dedicated TI-determining sequence (Look-Locker) and ranged from 220 to 300 ms. Contiguous

end-diastolic short-axis slices of the left ventricle (LV) were obtained from base to apex without gaps (8 ~ 10 slices in number) to cover the whole LV.

4. MRI data analysis

Left ventricle volume, and mass were measured by cine image with commercially available software (MASS, Medis, Netherlands). Infarcted wall thickness was measured with enhanced segment of delayed enhancement imaging at end-diastolic phase.

Hyperenhancement areas were automatically traced on short axis delayed hyperenhancement images, except the most basal and apical slices, and measured by commercial software (Viewforum, Philips Medical systems, Netherlands). Relative infarct LV mass (%) was defined as infarcted LV mass/total LV mass. Persistent microvascular obstruction (MVO) was defined as the hypoenhanced area within hyperenhanced area.

5. Statistical analysis

All data were expressed as mean (SD). The serial changes of plasma adiponectin were compared by a paired *t* test and repeated measures ANOVA. Correlation between adiponectin levels and the indicated parameters were examined by Pearson's coefficient of correlation. Because distributions of adiponectin were skewed, logarithmically transformed values were used for statistical analysis. Values of $p < 0.05$ were considered significant.

III. RESULTS

A total of 31 patients who underwent successful coronary stenting after ST-segmented elevation AMI and performed CMRI were enrolled. Clinical characteristics of patients are listed in Table 1. Patients were 60 ± 12 years of age (range 46 to 87). Mean body mass index was 25.0 ± 2.7 kg/m^2. 48.4% of patients were diagnosed as having hypertension and 19.3% of patients had diabetes. The average of peak creatine kinase leakage was 305 ± 217 mg/dl. Relative infarct mass as assessed by CMRI was 23.7% ± 13.7%. The ejection fraction measured by echocardiography was 49.6% ± 8.3%. (Table 1).

Table 1. Baseline characteristics of patients

	(N=31)
Age (years)	60± 12
Gender (M:F)	23:8
BMI (kg/m^2)	25.0 ± 2.7
Diabetes mellitus	6 (19.3%)
Smoking	19 (61.3%)
Hypertension	15 (48.4%)
Pain-to-balloon time (minutes)	225 ± 119
Severity of coronary artery disease	
1VD	12 (38.7%)
2VD	11 (35.5%)
3VD	8 (25.8%)
Culprit lesion	
Left anterior descending artery	12 (38.7%)
Left circumflex artery	7 (22.6%)
Right coronary artery	12 (38.7%)
Total cholesterol (mg/dl)	188 ± 33.1
HDL cholesterol (mg/dl)	41.7 ± 10.2
LDL cholesterol (mg/dl)	112.7 ± 31.1
Triglyceride (mg/dl)	126.7 ± 86.7
Peak CK-MB (mg/dl)	305 ± 217
hsCRP (mg/L)	1.5 ± 1
Ejection fraction (%)	49.6 ± 8.3
Total LV mass (mm^3)	123843 ± 31505
Infarct mass (mm^3)	31547 ± 23398
Relative infarct mass (%)	23.7 ± 13.7
Microvascular obstruction (mm^3)	2786 ± 6167
Relative MVO (%)	1.7 ± 3.8

VD : vessel disease, hsCRP : high sensitive CRP,
HDL : high-density lipoprotein, LDL : low-density lipoprotein
LV : left ventricle, MVO : microvascular obstruction

The serial changes of plasma adiponectin level during the 3 days after the acute myocardial infarction were examined. The average of plasma adiponectin level on admission was 5.3 ± 4.1㎍/ml. There is no significant change of plasma adiponectin level in the process of time. (Table 2)

Table 2. Time course of plasma adiponectin level (n=31)

Sampling time	Adiponectin level (㎍/ml)	P value
On admission	5.3 ± 4.1	
6 hours after primary PCI	5.3 ± 4.4	NS
24 hours after primary PCI	5.4 ± 4.5	NS
48 hours after primary PCI	5.7 ± 4.9	NS
72 hours after primary PCI	5.6 ± 4.0	NS

NS : not significant. PCI : Percutaneous coronary intervention.
p value is compared with admission.

Plasma adiponectin concentration showed significant correlation with the level of cholesterol on adimission. All of the plasma concentrations of adiponectin from 0 to 72hrs after PCI correlated positively with initial HDL-cholesterol ($r = 0.45$, $p < 0.05$) and correlated negatively with initial triglyceride ($r = -0.41$, $p < 0.05$), but not with total cholesterol and LDL cholesterol. (Table 3)

To distinguish factors associated with adiponectin concentration, the relation between adiponectin levels and cardiac parameters determined by CMRI were studied. Any of the adiponectin levels did not significantly correlate with a relative infarct mass or relative microvascular obstruction. (Table 4)

Table 3. Correlation of log adiponectin levels and clinical characteristics (Age, sex, BMI adjusted)

	Admission		6 hours after PCI		24 hours after PCI		48 hours after PCI		72 hours after PCI	
	coefficient	P value	coefficient	P value	coefficient	P value	coefficient	P value	coefficient	P value
Total cholesterol (mg/dl)	0.18	NS	0.15	NS	0.18	NS	0.15	NS	0.16	NS
HDL cholesterol (mg/dl)	0.45	<0.05	0.43	<0.05	0.46	<0.05	0.45	<0.05	0.4	<0.05
LDL cholesterol (mg/dl)	0.15	NS	0.11	NS	0.12	NS	0.09	NS	0.11	NS
Triglyceride (mg/dl)	-0.41	<0.05	-0.45	<0.05	-0.5	<0.01	-0.5	<0.05	-0.44	<0.05
Peak CK-MB (mg/dl)	0.17	NS	0.15	NS	0.16	NS	0.13	NS	0.2	NS

NS : not significant, BMI : body mass index, HDL : high-density lipoprotein, LDL : low-density lipoprotein, CK : creatine kinase

Table 4. Correlation of log plasma adiponectin levels and cardaic parameters (Age, sex. BMI adjusted)

	Admssion		6 hours after PCI		24 hours after PCI		48 hours after PCI		72 hours after PCI	
	coefficient	P value	coefficient	P value	coefficient	P value	coefficient	P value	coefficient	P value
Ejection fraction (%)	-0.07	NS	-0.06	NS	-0.14	NS	-0.11	NS	-0.12	NS
Relative infarct mass (%)	-0.07	NS	-0.05	NS	0.001	NS	-0.01	NS	-0.004	NS
Relative MVO (%)	-0.13	NS	-0.17	NS	-0.15	NS	-0.18	NS	-0.13	NS

NS : not significant, BMI : body mass index, MVO : Microvascular obstruction

IV. DISCUSSION

In this study, the association between plasma adiponectin and CMRI parameters, such as infarct size and MVO were assessed. This study indicated that plasma adiponectin in 31 subjects for a period of up to 72hrs after PCI as a marker of myocardial damage had no corrleation with infarct size, MVO, and LVEF. Thus, plasma adiponectin levels after AMI might be neither a useful biomarker nor a prognostic factor for detecting myocardial damage.

Although the physiological role of adiponectin remains unclear, previous studies reported that adiponectin inhibited the expression of adhesion molecules in the vascular endothelium and release of cytokine from macrophages.[10,11] Therefore, adiponectin was thought to involve inflammation. Inflammation promotes the rupture of plaque that leads to thrombosis and acute coronary syndrome. The current hypothesis stated that chronic inflammation associated with coronary artery disease inhibited production of adiponectin. However, outside the context of diseases associated with obesity, an inflammatory status was not necessarily correlated with low adiponectin levels. Actually, the opposite was observed, with adiponectin levels increasing during inflammatory conditions.[12] Thus, adiponectin was regulated in the opposite direction. Therefore, the level of plasma adiponectin was low in the patient who had severe atherosclerosis and it still decreased right after AMI. However, it could be recovered as a result of inflammation caused by AMI.

Recently, Kojima *et al.* studied the correlation of adiponectin and CRP levels in AMI, and the result suggested that adiponectin might play a role in the inflammatory

process.[13] However, it is still unclear how plasma adiponectin affects acute coronary syndrome. In this study, to demonstrate the controversial factor, the association between adiponectin and the prognosis of AMI by using CMRI were analyzed. Consistent with previous data, this investigation showed that plasma adiponectin was inversely correlated with BMI and triglyceride, but positively correlated with HDL cholesterol.[14,15] However, the plasma concentration of adiponectin did not change significantly after AMI. Even though it did not show statistical significance, the level of plasma adiponectin tended to slightly increased. Furthermore, adiponectin did not correlate with any of the cardiac parameters estimated by CMRI.

Kojima *et al.* provided data to support the idea that during the course of myocardial infarction (from admission to 72 hours), the plasma adiponectin significantly reduced. They tried to explain this relation by two different processes. Plasma adiponectin concentrations might decrease as a result of the rupture of coronary plaques (consumption theory). An alternative explanation was that the inflammatory process might accelerate in subjects with low plasma adiponectin before the onset of AMI. Contrast to their result, this study showed a modest increase of adiponectin as time passed by after the primary PCI. Although the mechanisms behind these contradictory outcomes were unclear, the discrepancy could be caused by several reasons. All the patients in this study underwent coronary stent insertion instead of thrombolytic therapy or ballooning. The coronary stent insertion might cause severe focal inflammation in the coronary artery, and the adiponectin level increased due to inflammation just after stent insertion. Another possible explanation was disparity of

baseline characteristics of patients such as BMI, past history, severity of disease, and age. However, baseline characteristics of the patients who enrolled in their study were not described, it was impossible to compare..

The hypothesis to explain why the level of plasma adiponectin did not decrease is the mechanism which control plasma adiponectin prefered to decrease the infarct size and myocardial damage. Therefore, plasma adiponectin level might increase or at least not decrease. Before AMI, severe chronic atherosclerosis might decrease adiponectin. However, in the hyper-acute phase of AMI, adiponetin needed to be increased for preventing further myocardial apoptosis and it was consumed immediately. In conclusion, the amount of adiponectin which newly produced was equal to that of already used up. This results in no significant change of the level of plasma adiponectin. Moreover, as time passed, the adipocytes, which have recovered from acute ischemic damage, could produce more adiponectin, and the level of adiponectin would be normalized or slightly higher than the normal range.

This study has several limitations. Only a relatively small number of patients have been registered, which may lead to inconclusive results especially in the multivariable linear analysis.

Performing CMRI after the remodeling of infarcted myocardium completed can be useful for evaluating the association of the long term prognosis of AMI patient and the function of adiponectin. Unfortunately, there is no specific guideline which leads us to decide the best time to perform CMRI in the acute phase of MI.

In addition, the difference between high molecular adiponectin and low molecular

adiponectin also needs to be considered. Because this process is unable to distinguish the two different adiponectins by, we can not figure out the exact mechanism of each different effect of adiponectin. The ELISA used in this study detects the globular and full-length isoforms. Recent studies demonstrated that adiponectin circulates as a trimer with each isoform playing a different biological role.[16] The proportion of isoform expression is altered in various physiological and pathological conditions. Newly developed adiponectin assays measure each isoform separately. Further research is needed to establish the role of the different isoforms in diverse pathologies.

In addition, we did not include patients who developed cardiogenic shock, because those patients whose vital signs were unstable and we could not perform the CMRI. Myocardial damage of enrolled patients was relatively mild.

V. CONCLUSION

In conclusion, this study showed no correlation between adiponectin level and infarct size during early phase of STEMI. It suggested contrary evidence that there is an association of adiponectin with adverse cardiovascular outcome in patients with AMI and preserved left ventricular systolic function. The clinical relevance of these findings needs further evaluation. These data should stimulate experimental and epidemiological studies to further elucidate the complex role of the adipocytokine, adiponectin in atherosclerosis and coronary artery disease.

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<ABSTRACT(IN KOREAN)>

급성심근경색에서 심근손상과 아디포넥틴과의 상관관계

<지도교수 최동훈>

연세대학교 대학원 의학과

이찬주

최근 아디포넥틴은 관상동맥질환의 위험성과 예후를 예측하는 것으로 여겨지고 있다. 그러나 아디포넥틴의 농도가 심근경색에서 생물학적 표지자로 유용하게 사용될 수 있는지는 확실하지 않다. 이번 연구에서 급성심근경색 후의 아디포넥틴 농도 변화와 자기공명영상을 이용하여 측정한 심근경색의 크기를 분석하여 아디포넥틴의 표지자로서의 유용성을 밝히고자 하였다.

급성심근경색 후에 일차적 경피적 관상동맥중재술 (primary percutaneous coronary intervention)을 성공리에 시행 받았던 환자 31명에게서 아디포넥틴 농도를 측정하였다. 채혈은 입원 직후와 관상동맥중재술 시행 6, 24, 48, 72시간 후에 이루어졌다. 자기공명영상으로 좌심실 부

피(LV mass), 경색 부피와 미세혈관폐색(microvascular obstruction)을 측정하였고 상대적 경색부피와 상대적 미세혈관폐색도 계산하였다. 좌심실 구혈률(LVEF)은 심초음파를 이용하여 구하였다.

급성심근경색 초기동안 아디포넥틴의 농도는 유의한 변화를 보이지 않았다. 심근경색 직후 아디포넥틴 농도는 고밀도 지단백 콜레스테롤과 양의 상관관계를 보였고($r = 0.45$, $p < 0.05$), 중성지방과는 음의 상관관계를 보였다. ($r = -0.41$, $p < 0.05$) 그러나 입원 후 72시간 동안 측정한 아디포넥틴은 상대적 경색부피, 상대적 미세혈관폐색 그리고 좌심실 구혈률과 상관관계를 보이지 않았다.

결론적으로, 이번 연구에서 급성심근경색 초기에 아디포넥틴의 농도는 심근경색의 크기와 무관하였다. 따라서 심근손상과 좌심실 구혈률을 예측하기 위한 표지자로서 아디포넥틴의 역할은 그 유용성에 대한 더 많은 연구가 필요하다.

핵심되는 말 : 아디포넥틴, 심근경색, 심장자기공명영상