Published in final edited form as:

Am J Cardiol. 2010 April 15; 105(8): 1147–1152. doi:10.1016/j.amjcard.2009.12.015.

Determinants of Adiponectin Levels in Patients with Chronic Systolic Heart Failure

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Abstract

Adiponectin, an adipocytokine, is secreted by adipocytes and mediates anti-hypertrophic and anti-inflammatory effects in the heart. Plasma concentrations of adiponectin are decreased in obesity, insulin resistance and obesity-associated conditions such as hypertension and coronary heart disease. However, a paradoxical increase in adiponectin levels is observed in human systolic heart failure (HF). We sought to investigate the determinants of adiponectin levels in patients with chronic systolic HF. Total adiponectin levels were measured in 99 patients with stable HF and left ventricular (LV) ejection fraction (EF) <40%. Determinants of adiponectin levels by univariate analysis were included in a multivariate linear regression model. At baseline patients were 62% black, 63% male, mean age of 60±13 years, LVEF of 21±9% and a body mass index (BMI) of 30.6±6.7kg/m². Mean adiponectin levels were 15.8±15μg/ml. Beta-blocker use, BMI, and blood urea nitrogen (BUN) were significant determinants of adiponectin levels by multivariate analysis. LV mass, structure, and LVEF were not related to adiponectin levels by multivariate analysis. Interestingly, the effect of beta-blocker therapy was most marked in non-obese patients with BMI < 30kg/m². In conclusion, in chronic systolic HF patients, beta-blocker therapy is correlated with lower adiponectin levels, especially in non-obese patients. This relation should be taken into account when studying the complex role of adiponectin in chronic systolic HF.

Keywords

Adiponectin; chronic systolic heart failure; beta-blockers

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Conflict of Interest:

None

Introduction

Adiponectin, an adipocyte-derived cytokine, is abundantly present in human plasma¹ and mediates favorable actions in cardiovascular and metabolic-associated diseases. Adiponectin exerts a plethora of effects including anti-hypertrophic and anti-inflammatory effects² in addition to improving vascular function and modulating pathological cardiac remodeling^{2,3}. Depressed adiponectin levels are evident in obesity, coronary artery disease (CAD), hypertension and insulin resistance^{3–5} and may reflect greater cardiovascular risk and inflammation. However increased adiponectin levels are seen in patients with systolic heart failure (HF)^{6–8}. The release of adiponectin into the circulation is associated with the severity of HF symptoms⁹, disease severity and mortality^{6,7}. Elevated adiponectin levels likely reflects an attempt to mitigate pro-inflammatory or impaired metabolic states and demonstrates a balance between protective and harmful pathways in left ventricular (LV) systolic dysfunction and HF. Interactions between various factors may alter adiponectin levels in HF patients, making it difficult to interpret adiponectin levels in the development and progression of HF. We therefore sought to investigate the determinants of adiponectin levels in a cohort of HF patients with chronic systolic dysfunction.

Methods

One hundred and four patients with chronic HF and LVEF <40% were recruited from an ambulatory HF clinic, at Boston Medical Center between 2001–2005. Five patients had end-stage renal disease and were on dialysis. They were excluded because adiponectin levels are positively associated with abnormal renal function¹⁰. Data was recorded at enrollment and the analysis reflects the measurements of 99 patients. A medical history was obtained to document etiology, severity of HF symptoms by New York Heart Association (NYHA) functional class and co-morbid disease. Routine laboratory results (e.g., electrolytes and blood count) and concomitant cardiac medications were recorded. Body mass index (BMI) was calculated as the ratio of weight to squared height. The Boston Medical Center Institutional Review Board approved the study. All patients gave written informed consent. *Ischemic etiology* was defined by a prior history of myocardial infarction (electrocardiogram/positive troponin), results of a positive non-invasive stress test, or cardiac catheterization. *Hypertensive etiology* was defined by a documented history of pharmacologically treated hypertension and no known CAD (by electrocardiogram, non-invasive stress test, or cardiac catheterization). *Idiopathic etiology* was defined as having no identifiable cause of the cardiomyopathy and included primary valvular disease, alcohol-induced and familial.

Two-dimensional and Doppler echocardiography were performed at baseline using the Vingmed Vivid Five System (GE Vingmed, Milwaukee, WI) as previously described¹¹. Echocardiograms were performed and analyzed in a blinded manner. As described previously measurements of systolic and diastolic chamber dimensions and wall thickness were obtained from two-dimensional imaging according to the recommendations of the American Society of Echocardiography¹¹. Similarly the standard cube formula was used to calculate LV mass. Relative wall thickness (RWT) was calculated as: $(2 \times \text{PWT}) / \text{LVEDD}$, where PWT is posterior wall thickness and LVEDD is LV end-diastolic diameter¹¹.

Vital signs were recorded and 35mL of fasting blood samples were collected from the antecubital vein after 10-minutes of rest in the supine position. Plasma/ serum was decanted and immediately stored at -80°C . Adiponectin and BNP levels were determined by ELISA (Otsuka Pharmaceutical Co Ltd) and the ADVIA Centaur assay (Siemens Healthcare Diagnostics) respectively. The minimal detection limit for adiponectin was $0.12 \mu\text{g/mL}$ and the intra- and interassay CVs were both <10%. CRP levels were measured by a commercial laboratory (Quest Diagnostics, Cambridge, MA).

Summary statistics are presented as mean±standard deviation for continuous variables and as number (percentage) for categorical variables. We examined the relationship between each marker and adiponectin using the Pearson's correlation. In these analyses, the skewed variables were analyzed after log transformation. Adiponectin levels were divided into terciles, and the relationship between adiponectin, clinical characteristics and echocardiography parameters were examined using ANOVA, or chi-square test, as appropriate. For medication use, we compared adiponectin levels between patients "using" or "not using" each class of medication by student *t* test. We specified a priori that a factor must show a potential association (i.e., $P < 0.15$) with adiponectin by bivariate analysis in order to be tested in a multivariable regression model. A value of $P < 0.05$ was considered statistically significant. All reported *P*-values are 2-tailed and all confidence intervals are computed at the 95% level. All analyses were conducted using SPSS software, version 11.5 (SPSS Inc, Chicago, Ill).

Results

Ninety-nine chronic, systolic HF patients completed the study. The majority of patients were black, predominantly men and had hypertension (Table 1). Patients were on evidence-based therapy for systolic HF and most were New York Heart Association (NYHA) Class II/III. At the time of enrollment, the mean duration with the diagnosis of HF for these patients was 4 years (range: 1 to 237 months). The majority of patients has a mean BMI $>30\text{kg/m}^2$. Mean creatinine was $1.7 \pm 2.3\text{mg/dl}$ with the MDRD GFR of $63.3 \pm 31\text{ml/min/1.73m}^2$. The mean adiponectin level was $15.8 \pm 15\mu\text{g/ml}$.

Adiponectin levels and BMI had a significant inverse correlation (Figure 1). Correlations with other clinical and echocardiography variables were nonsignificant, except for LV posterior wall and LV septal thickness ($r = -0.27$, $P = 0.007$ and $r = -0.24$, $P = 0.016$, respectively), blood urea nitrogen (BUN; $r = 0.29$, $P = 0.003$) and creatinine clearance ($r = -0.31$, $P = 0.003$). Table 2 shows the variables across adiponectin terciles. The lowest tercile of adiponectin levels was seen in the most obese patients. Similarly, adiponectin levels were significantly associated with BUN across the terciles. The other variables were not significantly associated with adiponectin.

The relation between adiponectin levels and medication used was investigated (Table 3). The use of beta-blockers (metoprolol or carvedilol) was significantly associated with adiponectin levels. Patients on beta-blockers had lower adiponectin levels than those patients not on beta-blockers. As shown in Figure 2, the effect of beta-blocker therapy on adiponectin levels was most marked in non-obese patients (BMI $< 30\text{kg/m}^2$). As expected higher adiponectin levels were seen in non-obese patients (Figure 1).

In multivariate linear regression, beta-blocker use, BMI, and BUN remained significant determinants of adiponectin levels (Table 4). LV mass, structure, LVEF, gender, age and race were not correlated with adiponectin levels in multivariate analysis.

Discussion

Our study demonstrated that in chronic, stable systolic HF patients, beta-blocker therapy was significantly correlated with lower adiponectin levels, especially in non-obese patients. BMI and renal function were also significant determinants of adiponectin values. The impact of medications, particularly beta-blockers, should be taken into account when evaluating adiponectin levels in patients with HF, as this finding may help to explain some of the divergent results from prior studies.

Normal adiponectin levels vary by race, gender and age^{12–14}. In normal non-obese Japanese subjects the mean value was $8.9 \pm 5.4\mu\text{g/ml}$ ¹²; in African American subjects it was $11.1 \pm 5\mu\text{g/ml}$ ¹³ and in Caucasian subjects the levels were somewhat higher, with value range of 11.7

$\pm 5.4 \mu\text{g/ml}$ to $17.3 \pm 10.4 \mu\text{g/ml}$ ¹⁵. Although adiponectin levels are not standardized and direct comparisons must be interpreted with caution, our diverse HF patient population had adiponectin levels within the normal range (mean levels were $15.8 \pm 15 \mu\text{g/ml}$) and comparable to other HF studies^{7,8,16}. However our study differed in the following manner. The HF patients studied by Kistorp and colleagues⁶ had a shorter duration of HF (median duration of HF was 6 months) whereas our patients had chronic HF with the median duration of HF of 28 months. Unlike other studies^{6,7}, the patient population in our study was heterogeneous (>50% were black, almost 40% were females and were obese) and more reflective of a chronic, ambulatory HF population.

Adiponectin levels are depressed in obesity, diabetes mellitus, insulin resistance and in CAD³⁻⁵. However adiponectin levels are elevated in patients with anorexia nervosa¹⁷ and in cardiac cachexia^{6,7}. Mean adiponectin levels were not depressed in our chronic HF population although these patients were overweight/obese. We speculate that this is possibly because of a compensatory response to the “stress” of HF – perhaps an attempt to mitigate adverse factors in LV remodeling in HF.

In normal subjects, the adult heart uses fatty acids as an energy source. This substrate is shifted from fatty acids to glucose utilization in the failing human heart. However if this shift is inadequate, the failing heart suffers from a state of chronic energy deprivation. Therefore adiponectin may be released by adipose tissue to compensate for this impaired metabolic state^{6,7}. Adiponectin improves both glucose metabolism and insulin resistance¹ via the AMPK signaling pathway¹⁸. Use of beta-blockers in HF patients may improve the metabolic profile by improving insulin sensitivity¹⁹. Interestingly, beta-blockers decrease adiponectin levels in patients with CAD²⁰, suggesting beta-blockers may mediate effects on adiponectin levels regardless of the presence of chronic HF. However, since adiponectin levels appear to be increased in HF patients, the pathophysiological importance of beta-blockers on adiponectin levels may be accentuated in this context. The lack of correlation between adiponectin and beta-blocker in the study by Kistorp et al, may be because only 31% of the HF patients received beta-blocker and for most of these patients beta-blocker was reportedly being uptitrated⁶. It would be interesting in this group of patients to determine adiponectin levels in those who achieved maximal tolerated doses of beta-blockers. Yamaji et al, also showed that carvedilol administration in HF patients was accompanied by decreased adiponectin and BNP levels and associated with improved LVEF²¹. Thus several human studies^{21,22} have suggested that increased adiponectin levels in human HF reflects an attempt of the body to compensate for impaired metabolism that is evident in human HF.

Chronic exercise may mediate effects on the adrenergic system that are comparable to that of beta-blockade²³. Chronic exercise training reduces adiponectin levels in patients with chronic HF and may be due to improved insulin resistance and the anti-inflammatory effects of exercise in chronic systolic HF²⁴. Therefore alterations in adrenergic activation may underlie, at least in part, the increase in adiponectin levels seen in HF patients.

BNP levels correlate with adiponectin levels in human HF^{6,21} and may modulate adiponectin signaling via a cGMP-mediated pathway in human adipocytes obtained from HF patients²⁵. Our study showed no change in BNP levels across the 3 terciles of adiponectin levels although patients in the highest tercile of adiponectin had the highest BNP levels. Similarly decreased adiponectin levels are correlated with high CRP levels in patients with obesity-linked complications²⁶. There was no association with the adiponectin terciles in our study likely because of small numbers, although the highest CRP levels were found in the lowest tercile of adiponectin.

Adiponectin levels are increased in renal failure and have been associated with increased mortality¹⁰. This relates to impaired clearance, because kidney transplantation decreases adiponectin levels. Thus HF, like renal disease, may be a state of “adiponectin-resistance” and reflects the attempt of increased adiponectin to mitigate vascular disease triggered by risk factors²⁷. It is possible that clearance of adiponectin is impaired in HF patients and may be due to relative changes in adiponectin receptors²⁸ but these will require further study. The presence of “non-depressed” adiponectin levels in our study may also reflect a disconnection between adiponectin and/or a dysfunction of adiponectin receptors with a resulting increase in adiponectin secretion in HF as a compensatory response.

Adiponectin resistance has been described by a small number of studies examining human tissue¹⁸ and animal models²⁹ but the mechanistic details have not been defined. Another possibility is that situation may be confounded in some chronic human disease states by the counter-regulation of poorly described adiponectin paralogues that may have overlapping functions with adiponectin³⁰.

The present study has several limitations. *First*, the sample size is relatively small, and additional prospective studies are necessary in a larger population. However, our patient population also represents a stable, chronic HF group, which is a representative HF population. *Second*, we did not measure pro-inflammatory cytokines such as TNF- α and IL-6, which are associated with adverse cardiac remodeling however CRP was measured. *Finally* it was not our objective to demonstrate the impact of adiponectin levels or the reduction of these levels by beta-blocker therapy on clinical outcomes and HF progression. We believe that would be an interesting focus for future studies.

Acknowledgments

This work was supported by National Heart Lung and Blood Institute (NHLBI) grants, Bethesda, Maryland, USA, HL-04423 (F.Sam) and HL079099 (F.Sam). Additional support was provided by an American Heart Association (AHA) Postdoctoral Fellowship Awards, Northeast Affiliate, Baltimore, Maryland, USA; (R.Shibata) and an AHA Scientist Development Grant, Northeast Affiliate, Baltimore, Maryland, USA; (N.Ouchi).

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Figure 1. Relationship between Adiponectin levels and Body Mass Index (BMI) in Chronic Systolic Heart Failure

Figure 2.

Effects of Beta-blocker therapy on Adiponectin levels according to Body Mass Index (BMI) in Chronic Systolic Heart Failure

Table 1**Demographics and Clinical Characteristics of Chronic Heart Failure Patients**

Characteristics	N = 99
Age (years)	60 ± 13
Men	62 (63 %)
Black	61 (62 %)
White	35 (35 %)
Hispanic	3 (3 %)
Body mass index (kg/m ²)	30.6 ± 6.7
Duration of heart failure (months) at enrollment	48 ± 50
Systolic blood pressure (mmHg)	125 ± 23
Diastolic blood pressure (mmHg)	72 ± 13
Heart rate (beats/minute)	75 ± 16
<i>Etiology of heart failure</i>	
Ischemic	38 (38 %)
Idiopathic	31 (32 %)
Hypertension	30 (30 %)
Diabetes mellitus	39 (39 %)
Hypertension	84 (85 %)
Chronic Renal Insufficiency	45 (45 %)
Gout	25 (25 %)
<i>Alcohol use</i>	
Active	40 (40 %)
Inactive	59 (60 %)
Smoker	22 (22%)
<i>New York Heart Association Functional Class</i>	
I	17 (18 %)
II	40 (40 %)
III	34 (34 %)
IV	8 (8%)
<i>Medication use</i>	
Angiotensin converting enzyme inhibitor /	87 (88%)
Angiotensin receptor blocker	
Beta-blocker	82 (83%)
Digoxin	51 (52%)
Spironolactone	13 (13%)
Nitrates	31 (31%)
Hydralazine	9 (9%)
Statin	50 (50%)

Continuous variables are described by mean ± SD and categorical variables by percentages (in parenthesis).

Table 2

Clinical, Biochemical and Echocardiography Variables across Adiponectin Terciles (n=99)

Variable	APN terciles			P-value
	1	2	3	
	(APN < 7.1 µg/ml)	(APN 7.1–13.6 µg/ml)	(APN >13.6 µg/ml)	
Age (years)	57 ± 14	60 ± 13	64 ± 12	0.12
Men	25 (76%)	15 (45%)	22 (67%)	0.45
Black	20 (61%)	15 (45%)	25 (76%)	0.21
Body Mass Index (kg/m ²)	34.3 ± 7.6	29.5 ± 6.3	27.9 ± 4.5	<0.001
Ischemic etiology	14 (42%)	14 (42%)	10 (30%)	0.31
Diabetes mellitus	15 (45%)	11 (33%)	10 (30%)	0.20
Hypertension	25 (76%)	26 (79%)	29 (88%)	0.21
Creatinine (mg/dl)	1.3 ± 0.6	1.4 ± 1.3	1.6 ± 0.9	0.58
Creatinine clearance (mL/min)	90 ± 43	87 ± 60	70 ± 37	0.18
Blood urea nitrogen (mg/dl)	25 ± 19	29 ± 23	40 ± 28	0.04
Brain natriuretic peptide (pg/ml)	375 ± 106	347 ± 254	421 ± 201	0.31
Hemoglobin (g/dl)	12.8 ± 1.6	12.5 ± 1.7	12.6 ± 1.7	0.73
C-reactive protein (mg/l)	10.8 ± 20	5.8 ± 8	6.5 ± 8	0.70
Systolic blood pressure (mmHg)	122 ± 22	130 ± 19	123 ± 28	0.33
Diastolic blood pressure (mmHg)	71 ± 15	71 ± 11	74 ± 15	0.56
Echocardiography parameters				
Left atrium (mm)	48 ± 8	45 ± 6	48 ± 6	0.15
Ventricular septal thickness (mm)	11 ± 2	10 ± 2	10 ± 2	0.14
Posterior wall (mm)	11 ± 2	10 ± 2	10 ± 2	0.27
Left ventricular end-diastolic diameter (mm)	64 ± 9	61 ± 9	64 ± 12	0.49
Left ventricular end-systolic diameter (mm)	50 ± 10	47 ± 11	53 ± 14	0.15
Left ventricular ejection fraction (%)	21 ± 8	23 ± 9	19 ± 10	0.14
Left ventricular mass (g)	300 ± 79	257 ± 80	270 ± 102	0.14
Relative wall thickness	0.17 ± 0.04	0.17 ± 0.04	0.16 ± 0.04	0.54

Continuous variables are described by mean ± SD and categorical variables by percentages (in parenthesis).

Table 3

Adiponectin Levels According To Medication Use

Medication	Number of Patients	Adiponectin level ($\mu\text{g/ml}$)	P-value
ACE-I / ARB	87	15.0 ± 13.7	0.44
Beta-blocker	82	13.2 ± 11.6	0.02
Spirolactone	13	17.4 ± 20.7	0.63
Statin	50	14.3 ± 14.8	0.41
Digoxin	51	14.6 ± 12.8	0.43

Table 4

Determinants of Adiponectin Levels on Multivariate Analysis.

Independent Variables	B coefficient	95% confidence interval	P-value
Beta-blocker use	-11.16	-17.9, -4.4	0.001
Body Mass Index	-.644	-1.07, -.022	0.003
Blood urea nitrogen	0.16	0.05, 0.27	0.005
Left ventricular mass	-0.026	-0.06, 0.009	0.15
Black race	3.97	-1.56, 9.49	0.16
Left ventricular ejection fraction	-21.30	-53.28, 10.67	0.19
Age	-0.058	-0.28, 0.16	0.59
Men	-0.98	-6.76, 4.80	0.74