Evaluation of serum adiponectin levels in patients with heart failure and relationship with functional capacity

Kalp yetersizliği olan hastalarda serum adiponektin düzeylerinin değerlendirilmesi ve fonksiyonel kapasite ile ilişkisi

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Objectives: We aimed to evaluate serum adiponectin levels in relation to the NYHA functional capacity class in patients with heart failure (HF).

Study design: The study included 49 patients (40 males, 9 females; mean age 63 years) with HF, whose functional capacity was NYHA class II to IV. Echocardiographic examination was performed and serum adiponectin levels were measured. The results were compared in relation to the NYHA classes and with those of 41 control subjects (24 males, 17 females; mean age 54.2 years) without HF.

Results: Functional capacity was NYHA class II in 13 patients (26.5%), class III in 23 patients (46.9%), and class IV in 13 patients (26.5%). Compared to the control group, the HF group exhibited a significantly higher mean age (p=0.001), lower body mass index (p=0.004), decreased left ventricular ejection fraction (EF) (33.2±7.7% vs. 64.9±4.3%; p=0.0001), and increased serum adiponectin level (4.0±3.2 µmg/dl vs. 2.4±2.3 µmg/dl; p=0.009). Both EF (p=0.001) and adiponectin level (p=0.004) showed significant differences between the NYHA groups, with the latter showing a sharp increase from 2.6±2.6 µmg/dl in class II to 6.8±3.7 µmg/dl in class IV. In all paired comparisons among the three NYHA groups, EF and serum adiponectin level exhibited significant differences except for the serum adiponectin level for NYHA class II and III (for NYHA class II and IV, p=0.003; for class III and IV, p=0.008). In correlation analysis, serum adiponectin level was in a significant inverse correlation with EF (r=-0.380, p=0.0001), and a positive correlation with the NYHA class (r=0.423, p=0.0001).

Conclusion: Serum adiponectin levels significantly increase in patients with HF, in parallel with deterioration in functional capacity and with significant decreases in EF.

Key words: Adiponectin/blood; biological markers; heart failure; ventricular function, left.

Amaç: Kalp yetersizliği (KY) olan hastalarda serum adiponektin düzeyleri NYHA fonksiyonel kapasite sınıflarına göre değerlendirildi.

Çalışma planı: Fonksiyonel kapasitesi NYHA sınıf II-IV olan, KY'li 49 hasta (40 erkek, 9 kadın; ort. yaş 63) çalışmaya alındı. Tüm hastalarda ekokardiyografik inceleme yapıldı ve serum adiponektin düzeyleri ölçüldü. Sonuçlar NYHA sınıfları arasında ve klinik ve ekokardiyografik olarak KY saptanmayan 41 kişilik (24 erkek, 17 kadın; ort. yaş 54.2) kontrol grubuyla karşılaştırıldı.

Bulgular: Fonksiyonel kapasite 13 hastada (%26.5) NYHA sınıf II, 23 hastada (%46.9) sınıf III, 13 hastada (%26.5) sınıf IV idi. Kontrol grubu ile karşılaştırıldığında, KY hastalarında ortalama yaş anlamlı derecede daha yüksek (p=0.001), beden kütle indeksi daha düşük (p=0.004), sol ventrikül ejeksiyon fraksiyonu (EF) daha düşük (%33.2±7.7 ve %64.9±4.3; p=0.0001), serum adiponektin düzeyi daha yüksek (4.0±3.2 İmgr/dl ve 2.4±2.3 µmgr/dl; p=0.009) bulundu. Sol ventrikül EF ve serum adiponektin düzeyi NYHA grupları arasında anlamlı farklılık gösterdi (p=0.001 ve p=0.004). NYHA sınıf II'de ortalama 2.6±2.6 İmgr/dl olan serum adiponektin düzeyi sınıf IV'de 6.8±3.7 µmgr/ dl'ye yükseldi. NYHA sınıflarının ikili karşılaştırmasında, EF ikili tüm gruplar arasında anlamlı farklılık gösterirken, serum adiponektin düzeyi, NYHA II-III grupları dışında, diğer gruplar arasında anlamlı derecede farklıydı (NYHA II-IV, p=0.003; NYHA III-IV, p=0.008). Korelasyon analizinde, serum adiponektin düzeyi EF ile anlamlı negatif ilişki (r=-0.380, p=0.0001), NYHA sınıfı ile anlamlı pozitif ilişki gösterdi (r=0.423, p=0.0001).

Sonuç: Kalp yetersizliği olan hastalarda serum adiponektin düzeyi anlamlı artış göstermekte ve bu artış fonksiyonel kapasite kötüleştikçe, EF'deki azalma ile birlikte, daha belirgin olmaktadır.

Anahtar sözcükler: Adiponektin/kan; biyolojik belirteç; kalp yetersizliği; ventrikül fonksiyonu, sol.

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In recent years, adipocytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-·) are also thought to be responsible for the pathogeneses of heart failure (HF) and its possible causes such as coronary artery disease (CAD), hypertension, diabetes mellitus, and obesity.[1,2] Although the physiological role of adiponectin which is released from adipose tissue has not been yet established, its anti-atherogenic and anti-inflammatory effects on endothelial cells and macrophages have been reported.[3-5] Serum adiponectin level has also been reported to decrease in the presence of diabetes mellitus, metabolic syndrome, obesity and CAD.[6-8] Normal or high serum adiponectin levels have been suggested to prevent the development of cardiovascular diseases and complications in healthy individuals.[9] Some recent studies have also demonstrated that serum adiponectin levels are paradoxically higher in patients with chronic heart failure, and that they were an independent predictor of mortality.[10,11]

In this study, we evaluated serum adiponectin levels according to the functional capacity classification in patients with HF.

PATIENTS AND METHODS

The study included 49 patients (40 males, 9 females; mean age 63.0±10.6 years) with ischemic or hypertensive HF, idiopathic cardiomyopathy or heart valve disease whose functional capacity was NYHA class II to IV, and 41 control subjects without HF as shown through clinical and electrocardiographic evaluation (24 males, 17 females; mean age 54.2±11.3). Of the 49 patients with HF, 16 had hypertension and 25 had diabetes mellitus, whereas 14 developed both.

Physical examination was performed and history obtained from both the patient group and controls. Patients with functional capacity of NYHA class I, chronic renal failure, and those with a known pulmonary disease such as chronic obstructive pulmonary disease were excluded from the study. All patients were receiving treatment for HF including diuretics, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB), and beta-blockers.

The 12-lead ECG of the patients was performed at rest and transthoracic echocardiographic assessment was obtained in the left lateral decubitus position in accordance with recommendations of the American Society of Echocardiography.[12] A 2.5 mHz probe and Vivid 7 echocardiography device (General Electric, Horton, Norway) was used during assessment. Two-dimensional echocardiography was used to estimate left ventricular ejection fraction (EF) by the Simpson's rule.

Routine biochemical analyses of all subjects were performed using 12-hour fasting venous blood samples. The collected samples for adiponectin were centrifuged at 4000 rpm for 7 minutes, and the supernatant obtained was stored at -20°C under laboratory conditions. Levels of serum total adiponectin were measured by ELISA method (Adiponectin ELISA, BioVendor Laboratory Medicine Inc., Czech Republic).

All patients were informed about the purpose of the study and informed consents were obtained from all patients. The study was approved by the local ethical committee of our hospital.

Statistical analysis. The SPSS program (Statistical Package for Social Sciences, v. 11.0 for Windows) was used for statistical analysis and the results were expressed as mean ± standard deviation. The Student t-test was used for comparison of quantitative data and in the assessment of subjects with/without HF, while Kruskal-Wallis test was used in the comparison of subgroups of HF patients according to their functional capacity (NYHA class II, III, IV). The Mann-Whitney U-test was used in paired comparison of control group and patient subgroups according to their functional capacity. Pearson correlation test was also used in the assessment of the correlation between serum adiponectin levels and certain parameters. $P<0.05$ was considered to be statistically significant.

RESULTS

CAD in 39 patients (79.6%), idiopathic cardiomyopathy in six (12.2%), hypertensive heart disease in two (4.1%), and other factors in two (12.2%) were responsible for heart failure. On the other hand, 13 patients (26.5%) were in NYHA class II, 23 patients (46.9%) were in NYHA class III, and 13 patients (26.5%) were in NYHA class IV.

The main characteristics of the patients and controls are summarized in Table 1. Compared to the control group, the HF group exhibited a significantly higher mean age (p=0.001) and a lower body mass index (p=0.004). On the other hand, no significant difference was found between the groups in terms of hypertension, diabetes mellitus and smoking history.

Left ventricular ejection fraction was within normal range in the controls, while it was significantly lower in the patient group (p=0.0001). The serum adiponectin levels were significantly higher in patients with HF (4.0±3.2 µmg/dL) compared to the controls (2.4±2.3 µmg/dL) (p=0.009). Fasting blood glucose level was significantly higher, while the total and HDL-cholesterol levels were significantly lower in the patient group,

Table 1. Comparison of clinical and laboratory findings and left ventricular ejection fraction of patients

	Patient Group (n=49)			Control Group (n=41)			
	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	*p*
Age			63.0±10.6			54.2±11.3	**0.001**
Sex							NS
Male	40	81.6		24	58.5		
Female	9	18.4		17	41.5		
Body mass index (kg/m^2)			26.9±4.3			29.8±4.8	**0.004**
Hypertension	16	32.7		17	41.5		NS
Diabetes Mellitus	25	51.0		14	34.2		NS
Cigarette smoking history	15	30.6		18	43.9		NS
Previous myocardial infarction	39	79.6		-			
Coronary artery bypass grafting	18	36.7		-			
Percutaneous coronary intervention	10	20.4		-			
Left ventricular ejection fraction (%)			33.2±7.7			64.9±4.3	**0.0001**
Adiponectin (μmg/dL)			4.0±3.2			2.4±2.3	**0.009**
Glucose (mg/dL)			138.4±53.1			110.4±44.0	**0.009**
Total cholesterol (mg/dL)			169.0±.35.0			185.3±28.7	**0.019**
HDL-cholesterol (mg/dL)			40.2±9.8			44.5±10.0	**0.045**
LDL-cholesterol (mg/dL)			102.2±28.0			104.4±22.5	NS
Triglyceride (mg/dL)			126.4±60.6			159.7±93.0	**0.05**
Creatinine (mg/dL)			1.0±0.3			0.8±0.12	NS
Hemoglobin (g/dL)			13.3±1.9			14.01±1.8	NS

NS: non-significant

compared to the control group. Plasma LDL-cholesterol level was not significantly different between the groups, whereas triglyceride level was significantly lower in patients with HF (Table 1).

Table 2 shows comparison of the left ventricular EF and serum adiponectin level based on NYHA classes. The EF (p=0.001) and adiponectin (p=0.004) level showed significant differences between the NYHA groups. The increase in adiponectin levels was also more apparent as the functional capacity worsened.

In all paired comparisons between the left ventricular EF and serum adiponectin level according to the NYHA groups, a significant difference was found between the groups in terms of left ventricular EF (p=0.04, p=0.001 and p=0.01 for NYHA II-III, II-IV and III-IV, respectively). On the other hand, no significant difference was found between the NYHA II and III groups in terms of serum adiponectin level, whereas there was a significant difference between the NYHA II-IV and III-IV groups (p=0.003 and p=0.008).

In all paired comparisons between the controls and each NYHA group in terms of age, left ventricular EF and serum adiponectin level, a significant difference was found in respect of all three parameters, apart from the age and serum adiponectin level in the NYHA II group (Table 2).

Table 2. Evaluation of left ventricular ejection fraction and serum adiponectin levels in patients with HF according to the NYHA classes and paired comparison analysis of NYHA classes and the control group

	NYHA II (n=13)	NYHA III (n=23)	NYHA IV (n=13)	*p*
Ejection fraction (%)	38.4±4.3	33.9±7.4	27.0±7.1	**0.001**
Adiponectin (μmg/dL)	2.6±2.6	3.2±2.1	6.8±3.7	**0.004**
Compared to controls	*p*	*p*	*p*	
Age	NS	**0.0001**	**0.005**	
Ejection fraction	**0.0001**	**0.0001**	**0.0001**	
Adiponectin	NS	**0.03**	**0.001**	

NS: non-significant

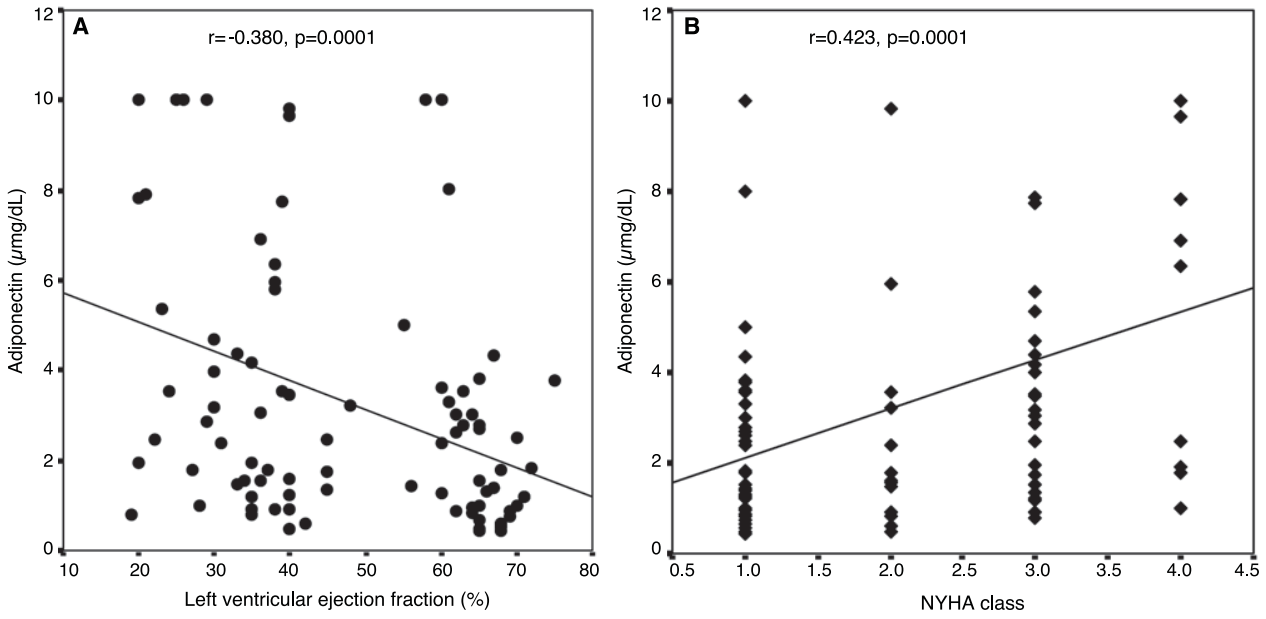

Figure 1. The relationship of serum adiponectin level with (A) left ventricular ejection fraction and (B) NYHA class.

In correlation analysis, serum adiponectin level was found to have a significant negative relationship with EF (r=-0.380, p=0.0001), and a positive correlation with the NYHA class (r=0.423, p=0.0001) (Figure 1). No significant difference was found between serum adiponectin level with age and BMI (r=0.204, p=0.06 and r=0.167, p>0.05, respectively)

DISCUSSION

Heart failure is currently the major cause of morbidity and mortality in adults. Several studies have demonstrated that neurohormonal activity resulting from a compensatory mechanism and increased cytokine at the beginning may have an adverse effect on prognosis of the disease in the later stage.[13-16] For instance, increased plasma catecholamine has been shown to be associated with increased morbidity and mortality in patients with HF.[13,14]

In our study, serum adiponectin levels were higher in patients with HF predominantly (79%) in those with a histology of ischemic disease compared to the controls (4.0±3.2 µmg/dL vs. 2.4±2.3 µmg/dL; p=0.009). In addition, serum adiponectin levels were significantly different in the patient groups based on their functional capacity (NYHA II-III-IV). The increase in adiponectin level was more apparent as functional capacity worsened. On the other hand, paired comparisons showed no significant difference but in the serum adiponectin levels between the NYHA II and NYHA III groups. Therefore, serum adiponectin levels can be suggested to increase significantly in patients with a poor functional capacity (NYHA III and IV), whereas no significant change was observed in patients with a better functional capacity (NYHA II). A recent study showed that serum adiponectin levels increased in 175 consecutive patients with chronic HF and that this increase was more apparent as the functional capacity worsened (NYHA). During 2-year-follow-up, serum adiponectin level was also shown to be an independent predictor of morbidity and mortality in the same study.[11]

Given that no significant difference was observed between the patient groups and controls in terms of the incidence of hypertension and diabetes mellitus and that there was no significant relation of serum adiponectin levels with age and BMI, serum adiponectin levels can be suggested to increase only due to HF. In other words, the increase in serum adiponectin level is not relative in patients with HF. On the other hand, several studies have also shown that serum adiponectin the level is not elevated, but is rather lower under such conditions.[6-9] According to the results obtained from several studies suggesting that serum adiponectin levels decreased in patients with CAD,[1,4,6] it is obvious that HF accounted for the increased adiponectin levels in patients with HF

of predominantly ischemic origin. Although mean BMI was significantly lower in patients with HF compared to the controls in our study, subjects in both groups were overweight. Therefore, although serum adiponectin level was reported to decrease in obese patients and to increase in the event of losing weight,[17] it was suggested that adiponectin levels were not significantly influenced by BMI in our study. The absence of a significant relationship between BMI and serum adiponectin levels also supports our conclusion. However, the objective and method of our study is insufficient to explain the reason for increased serum adiponectin level in HF patients. On the other hand, it can be suggested that increased serum adiponectin levels have protective effects to provide adequate hemodynamic in patients with HF as seen with the compensatory increased in plasma catecholamine. Whether the increase in serum adiponectin level in patients with HF is hazardous (toxic) similar to the increased plasma catecholamine is still not known. Although increased serum adiponectin levels did not predict the development HF in a study including 946 male adults without HF at baseline,[18] several studies showed that serum adiponectin levels increased in patients with chronic HF and that increased levels were independent predictor of mortality.[10,11] In another study including 449 consecutive patients with chronic HF having various BMI (<21, 21-25 and >25 kg/m2) groups evaluated serum total and high molecular weight (HMW) adiponectin levels, atrial (ANP), brain (BNP) natriuretic peptides and NT-proBNP levels, and total adiponectin levels were found to be independent prognostic predictor in all groups.[19] In addition, subgroup analysis found serum NT-proBNP (p=0.017) and plasma total adiponectin levels (p=0.003) to be prognostic predictor in only subjects with normal BMI. Authors concluded that measurement of total adiponectin level was more useful than of HMW adiponectin level in establishing the mortality risk and that plasma total adiponectin level was an independent prognostic predictor in HF patients with particularly normal BMI.[19]

Similar to our study, Nakamura *et al*.[20] also showed that serum adiponectin levels increased as the functional capacity worsened in HF patients. In another study including 138 patients with HF, Takano *et al*.[21] investigated adiponectin levels through sampling blood from the aorta, coronary sinus and peripheral vein and found that adiponectin levels significantly increased from aorta towards the coronary sinus. The authors also reported that the difference of adiponectin levels in coronary sinus and aorta was positively associated with adiponectin levels in blood samples obtained from peripheral vein. In this study, authors investigated whether adiponectin level affected cardiac tissue in HF patients. Another study including patients with dilated cardiomyopathy investigated cardiac adiponectin system through endomyocardial biopsy.[22] The authors found intact adiponectin receptors in the cardiac tissue, and decreased adiponectin mRNA and protein regulation. In the study, adiponectin injected into neonatal rats in vitro was shown to led to activation of pro-survival kinase and nitric oxide synthase, thereby preventing stress-induced apoptosis of cardiomyocytes.[22] In this study, adiponectin was suggested to be useful in the treatment of dilated cardiomyopathy in the future.

Decreased left ventricular EF is well known as one of the markers of poor prognosis of CAD.[23] In our study, we found significant difference between the groups in terms of left ventricular EF and the EF decreased as the functional capacity worsened. In addition, a significantly negative relation was found between serum adiponectin level and left ventricular EF (r=0.380, P=0.0001). On the other hand, George *et al*.[11] did not find any significant relationship between serum adiponectin level and left ventricular EF, but however found a significant association with the functional capacity (NYHA) and serum adiponectin level, similar to our study. Analyses performed to identify the possible relation between serum adiponectin level and left ventricular EF among the patient groups including those with functional capacity (NYHA classes) and controls found no significant difference in the serum adiponectin level only in patients with NYHA II class and controls, whereas serum adiponectin levels significantly increased in the other patient groups compared to the controls. However, we observed a significantly decreased left ventricular EF among all patient groups compared to the controls. In conclusion, it can be suggested that there is no significant difference between the HF patients with functional capacity of NYHA II and the controls in terms of serum adiponectin level, whereas serum adiponectin levels markedly increased in HF patients with NYHA III and IV.

A recent study showed that serum adiponectin levels increased in the elderly (>70 years) with a significant increase particularly in patients with HF of non ischemic origin. The study also found increased serum adiponectin levels to be increased mortality.[24] Another experimental study on animals models suggested that adiponectin improved systolic dysfunction following myocardial infarction, suppressed cardiac hypertrophy and interstitial fibrosis, and that it protect the myocardium against myocyte and capillary loss.[25]

In conclusion, serum adiponectin levels significantly increase in patients with HF compared to the controls

and the levels are associated with functional capacity of the patients. Serum adiponectin levels increase as the functional capacity worsens in this patient population. It can be concluded that there is no significant difference between the HF group with NYHA II of functional capacity and controls in terms of serum adiponectin levels, whereas levels significantly increased in HF patients with NYHA III and IV, compared to controls. Serum adiponectin level is also reported to be associated with the left ventricular EF and there is a marked increase in the levels as EF decreases.

Despite of all studies on adiponectin, whether its increase should be prevented and adiponectin receptor blockers should be developed and used in the treatment of HF patients is still unknown. Further studies are needed to elaborate on this subject.

REFERENCES

1. Sukhija R, Fahdi I, Garza L, Fink L, Scott M, Aude W, et al. Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. Am J Cardiol 2007;99:879-84.
2. Koch W, Kastrati A, Böttiger C, Mehilli J, von Beckerath N, Schömig A. Interleukin-10 and tumor necrosis factor gene polymorphisms and risk of coronary artery disease and myocardial infarction. Atherosclerosis 2001; 159:137-44.
3. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
4. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96:939-49.
5. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003;278:45021-6.
6. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
7. Salmenniemi U, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen K, et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 2004;110:3842-8.
8. Sheng T, Yang K. Adiponectin and its association with insulin resistance and type 2 diabetes. J Genet Genomics 2008;35:321-6.
9. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. Pharmacol Res 2007;56:459-67.
10. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005;112:1756-62.
11. George J, Patal S, Wexler D, Sharabi Y, Peleg E, Kamari Y, et al. Circulating adiponectin concentrations in patients with congestive heart failure. Heart 2006; 92:1420-4.
12. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358 67.
13. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87(6 Suppl):VI5-16.
14. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819-23.
15. Çelik T, İyisoy A, Çelik M, Yüksel UC, Kardeşoğlu E. C-reactive protein in chronic heart failure: a new predictor of survival. Int J Cardiol 2009;135:396-7.
16. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000;355:1126-30.
17. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
18. Ingelsson E, Risérus U, Berne C, Frystyk J, Flyvbjerg A, Axelsson T, et al. Adiponectin and risk of congestive heart failure. JAMA 2006;295:1772-4.
19. Tsutamoto T, Tanaka T, Sakai H, Ishikawa C, Fujii M, Yamamoto T, et al. Total and high molecular weight adiponectin, haemodynamics, and mortality in patients with chronic heart failure. Eur Heart J 2007;28:1723-30.
20. Nakamura T, Funayama H, Kubo N, Yasu T, Kawakami M, Saito M, et al. Association of hyperadiponectinemia with severity of ventricular dysfunction in congestive heart failure. Circ J 2006;70:1557-62.
21. Takano H, Obata JE, Kodama Y, Kitta Y, Nakamura T, Mende A, et al. Adiponectin is released from the heart in patients with heart failure. Int J Cardiol 2009; 132:221-6.

22. Skurk C, Wittchen F, Suckau L, Witt H, Noutsias M, Fechner H, et al. Description of a local cardiac adiponectin system and its deregulation in dilated cardiomyopathy. Eur Heart J 2008;29:1168-80.
23. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87(6 Suppl):VI17-23.
24. Haugen E, Furukawa Y, Isic A, Fu M. Increased adiponectin level in parallel with increased NT-pro BNP in patients with severe heart failure in the elderly: A hospital cohort study. Int J Cardiol 2008;125:216-9.
25. Shibata R, Izumiya Y, Sato K, Papanicolaou K, Kihara S, Colucci WS, et al. Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol 2007;42:1065-74.