The Association Between Carbohydrate Antigen 125 and Clinical Severity of Heart Failure

Karbonhidrat Antijen 125 ve Kalp Yetersizliğinin Klinik Şiddeti Arasındaki İlişki

Tuğba DÜBEKTAŞ CANBEK

Muğla Sıtkı Koçman Training and Research Hospital. Department of Internal Medicine, Muğla

Abstract

Carbohydrate antigen (CA) 125 and brain natriuretic peptide (BNP) levels increase in patients with heart failure (HF). In this study, we aimed to investigate CA 125 and pro-BNP levels in patients with HF and evaluate possible relationship between these biomarkers and functional capacity. A total of 48 patients were involved in the study (28 men, 20 women). They were aged 67.6 years on average. HF was diagnosed based on medical history, physical examination, electrocardiography, telecardiography and transthoracic echocardiography. The clinical statuses of all patients were assigned by being used NYHA classification. Patients with HF were categorized into two groups according to NYHA classification: Group B was with mild-moderate HF (I and II) (a total of 20 patients, 12 men and 8 women, aged 65 on average) and Group A was with severe HF (III and IV) (a total of 28 patients, 16 men and 12 women, aged 70.2 on average). The mean age was 70.2 years and 65 years in Group A and Group B, ($p = 0.078$). The mean EF was 28±10% in Group A, while the mean EF was 32±11% in Group B ($p=0.0012$). Serum CA 125 and Pro BNP levels in group A (CA 125=176.38 U/ml, and Pro BNP=36465.06 pg/ml) were found significantly higher than those in group B (CA 125=50.7 U/ml and Pro BNP=122.65 pg/ml) ($p<0.001$). CA 125 and pro BNP are a promising biomarker in the assessment of heart failure patients. There was a statistically significant relationship between CA 125 serum level and HF stage.

Keywords: CA 125, Pro BNP, Heart failure, Left ventricle, Markers

Öz

Kalp yetmezliği (KY) olan hastalarda karbonhidrat antijeni (CA) 125 ve brain natriüretik peptidi (BNP) seviyeleri artar. Bu çalışmada KY'li hastalarda CA 125 ve BNP düzeylerini araştırmayı ve bu biyomarkerlar ile fonksiyonel kapasite arasındaki olası ilişkiyi değerlendirmeyi amaçladık. Çalışmaya toplam 48 hasta dahil edildi (28 erkek, 20 kadın). Ortalama yaş 67.6. KY tanısı, anamnez, fizik muayene, elektrokardiyografi, telekardiyografi ve transtorasik ekokardiyografi ile konuldu. Tüm hastaların klinik durumları NYHA sınıflandırması kullanılarak belirlendi. KY'li hastalar NYHA sınıflamasına göre iki gruba ayrıldı: B grubu hafif-orta KY' li (I ve II) hastalar (toplam 20 hasta, 12 erkek ve 8 kadın, ortalama 65 yaş) ve A grubu ağır KY' li (III ve IV) (toplam 28 hasta, 16 erkek ve 12 kadın, ortalama 70,2). Ortalama yaş Grup A ve Grup B'de 70.2 ve 65 idi ($p=0.078$). Ortalama EF, Grup A'da %28±10 iken, Ortalama EF, Grup B'de %32±11 idi ($p=0.0012$). Grup A'daki serum CA 125 ve Pro BNP düzeyleri (CA 125=176.38 U/ml ve Pro BNP=36465.06 pg/ml), B grubunda (CA 125=50.7 U/ml ve Pro BNP=122.65 pg/ml) anlamlı derecede yüksek bulundu. ($p<0.001$). CA 125 ve pro BNP, kalp yetmezliği hastalarının degerlendirmesinde umut verici bir biyobelirteçtir. CA 125 serum seviyesi ile HF evresi arasınsa istatistiksel anlamlı ilişki vardır.

Anahtar Kelimeler: CA 125, Pro BNP, Kalp Yetmezliği, Sol Ventrikül, Marker

Introduction

It is well-established that brain natriuretic peptide (BNP) level is useful in the diagnosis, management and prognosis of heart failure (HF). Increased pro-BNP levels in the asymptomatic or initial stage of the disease indicate high sensitivity of BNP in the early diagnosis. Tumor biomarkers, which are synthesized and released by cancer cells, are produced as host response against cancer tissues. These biomarkers can be identified in circulatory system, body spaces, cell membranes, cell cytoplasm or nuclei. Carbohydrate antigen (CA) 125 is a common biomarker which is used in diagnosis, management and prognosis of oncological diseases (1,2). In recent years, serum CA 125 has been reported to be increased in patients with HF (4-9). In addition, the previous studies reported that CA 125 was associated with long-term mortality in patients with HF. (10,11)

In this study, we aimed to investigate CA 125 and pro-BNP levels in patients with HF and to evaluate possible relationship between these biomarkers and functional capacity.

	ORCID No
Tuğba Dübektaş CANBEK	0000-0002-3730-0029

Başvuru Tarihi / Received: 04.04.2019
Kabul Tarihi / Accepted : 08.07.2019

Adres / Correspondence : Tuğba DÜBEKTAŞ CANBEK
Muğla Sıtkı Koçman Training and Research Hospital. Department of Internal Medicine, Muğla
e-posta / e-mail : tugbadubektas80@hotmail.com

Materials and Method

Between May 2010 and December 2010, a total of 48 patients (28 males, 20 females; mean age: 67.6 years; range, 43 to 91 years) with HF were admitted to coronary intensive care unit (ICU) of the second internal medicine outpatient clinic at Izmir Tepecik Training and Research Hospital. Approval for the study was given by the regional Ethics Committee (Decision no: 11/VII; 17.06.2009). Detailed history was obtained from all patients. Physical examination, complete blood count, and biochemistry tests including glucose, blood urea nitrogen (BUN), creatinine, liver enzymes, lipid

profile, and electrolytes were performed. Blood samples were collected to analyse pro-BNP and CA 125 levels. The diagnosis of HF was based on medical history, physical examination findings, electrocardiographic (ECG), telecardiographic, and transthoracic echocardiographic (TTE) findings. The left ventricular systolic function (LVSF) was assessed through the LV ejection fraction (EF). All patients had an EF<45%. Clinical status of the patients was established using the New York Heart Association (NYHA) functional classification. Patients were divided into two groups based on the NYHA class: Group A including patients with severe HF (NYHA Class III-IV) and Group B including patients with mild to moderate HF (NYHA Class I-II). Group A consisted of 28 patients (16 males, 12 females; mean age: 70.2 years); group B consisted of 20 patients (12 males, 8 females; mean age: 65 years). Patients with renal failure, chronic hepatic impairment, chronic obstructive pulmonary disease, myocardial infarction (within the past six months), infections, inflammatory diseases, sepsis, malignancies, arthritis and connective tissue disorders, and hematological diseases were excluded. The local ethical committee approved the study protocol.

Echocardiographic assessment:

Transthoracic echocardiography (HDI-ATL Ultrasound) was performed on the first day of hospitalization. Measurements were taken by standard two-dimensional protocols according to guidelines of the American Society of Echocardiography (12). The LV end-systolic diameter (LVESD) and LV end-diastolic diameter (LVEDD) were measured by TTE. In general, LV dimensions were measured with 2D-guided M-mode from the parasternal projections, using a leading edge to leading edge convention. The LVEF was calculated using the Simpson's method. Pulmonary artery pressure (PAP) was assessed by non-invasive standard approach, whereas peak tricuspid regurgitation velocity was measured by continuous-wave Doppler. 3.2

Blood collection and testing:

Only on the first day of hospitalization, a 5-mL venous blood sample was drawn from the antecubital vein under sterile conditions without an anticoagulant. Blood samples were studied using Immulite 2000 DPC (Diagnostic Products Corporation, LA, USA) analyser. Tumor biomarkers were identified using specific CA 125 commercial kits (Diagnostic Products Corporation, LA, USA). The Immulite 2000 DPC assay is solid-phase two-site chemiluminescent immunoassay.

Laboratory BNP testing:

BNP levels were analyzed by a specialist who was blinded to the clinical characteristics of the patients. Blood samples were collected into tubes containing EDTA, centrifuged to separate serum and plasma, and stored at -20°C.

Samples were studied using the pro-BNP kit, a sandwich enzyme immunoassay in the E170 analyser. Pro-BNP, which is a polyclonal pro-BNP antibody labelled with biotinylated polyclonal pro-BNP antibody and ruthenium, forms a sandwich complex. With respect to the relationship between streptavidin and biotin, additive streptavidin-coated microparticles lead to binding to the complex solid phase. Reaction mixture is aspirated on the surface of an electrode with magnetic microparticle aggregation. Then, chemiluminescence emission measurement was performed by applying a voltage to the electrode. The results are determined by means of a calibration curve.

Statistical analysis:

Statistical analysis was performed using SPSS v11.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze whether the data were distributed normally. The Chi-square test was performed to compare percentages between the groups, while the Student t-test, Mann-Whitney U, and Wilcoxon W test was used to compare continuous variables between the groups. A two-tailed p value of <0.05 was considered statistically significant.

Results

The mean age was 70.2 years and 65 years in Group A and Group B, respectively, indicating no statistically significant difference (p=0.078). Of the patients, 12 were females and 16 were males in Group A, while eight were females and 12 were males in Group B. However, it did not reach statistical significance (p=0.843).

Baseline demographic characteristics of the patients in both groups and p values are shown in (Table 1) On the other hand, no statistically significant difference in the systolic blood pressure (SBP), diastolic blood pressure (DBP), BUN, creatinine, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) was observed between the groups. However, five patients were diabetics in Group A, while all patients were non-diabetics in Group B, indicating a statistically significant difference (16.6% vs. 0%, respectively; p<0.001).

The mean EF was 28±10% and the mean LVEDD was 69.9±9 cm in Group A, while the mean EF was 32±11% and the mean LVEDD 66.6±6 cm in Group B. There was a statistically significant difference in the mean EF values between the groups (p=0.0012). CA 125 was significantly higher in group A when compared with Group B (Table 2).

A total of 56% of the patients were on angiotensin converting enzyme (ACE) inhibitors, 62% on diuretics, 23% on aldosterone antagonists, 75% on digoxin, and 18 on nitrates. None of the patients received non-steroidal anti-inflammatory

drugs (NSAIDs). There were no differences between groups regarding drug use.

Table 1. Baseline demographic characteristics of the patients

	Group A (n = 28)	Group B (n = 20)	p
Age	70.2	65	0.078
Gender (Male)	57%	60%	0.843
SBP (mmHg)	119±20	114±9	0.057
DBP (mmHg)	76±11	73±7	0.075
DM	11 (39%)	6 (30%)	0.021
BUN (mg/dL)	59.6	41.3	0.043
Creatinin (mg/dL)	1.2	1.1	0.096
T.Cholesterol (mg/dL)	162.9	175.6	0.086
Triglycerid (mg/dL)	116.9	116.9	0.98
LDL (mg/dL)	101.7	111.3	0.67
HDL (mg/dL)	39.6	39.1	0.06

BUN: blood urea nitrogen, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, SBP: systolic blood pressure

Table 2. Laboratory and echocardiographic characteristics of the patients

	Group A	Group B	p
CA 125 (U/ml)	176.38	50.7	<0.001
Pro BNP (pg/ml)	36465.06	122.65	<0.001
LVEF %	26±10	32±12	0.012
LVDD	69±9	66±6	0.023

BNP: brain natriuretic peptide, CA: Carbohydrate antigen, LVEF: left ventricular ejection fraction, LVDD: left ventricular diastolic diameter

Discussion

Similar to previous studies, this study showed increased serum CA 125 and pro-BNP levels in patients with HF. However, we found higher CA 125 levels in patients with severe HF compared to those with mild to moderate HF, and pro-BNP was considered to be helpful to confirm the left HF with a significant difference among the patients with severe and mild to moderate HF.

Carbohydrate antigen 125 is a sensitive, however, non-specific tumor biomarker which is useful in the diagnosis, assessment of the treatment efficacy, and follow-up as well as early detection of recurrence (13). Recent studies have demonstrated that there is a relationship between hemodynamic status and elevated CA 125 levels in patients with HF (4,7,9,14). In a study including 77 patients with HF, Kouris et al. evaluated the relationship between HF functional class and tumor biomarkers (8). The authors reported increased CA 125 levels in these patients. In addition, they suggested that increased CA 125 was associated with functional class. In their study, the authors also investigated the possible relationship between increased CA 125 levels and echocardiographic parameters and found a weak association between CA 125 levels and the right ventricular pressure and renal functions. There was no relationship between CA 125 and E-wave deceleration time, LVEF, LVEDD, liver functions, and medical treatments. Consistent with previous study findings, we observed that serum CA 125 and pro-BNP levels were associated with the functional class of HF.

Effusion may be present in the underlying pathophysiological mechanism of increased CA 125 levels in heart failure (14-16). In a study, including 57 HF patients with varying etiologies in Seo et al. (14) reported that 65% patients had increased CA 125 levels. The authors observed that a higher number of patients with effusion had increased CA 125 levels. The levels were reduced or returned to normal by decreased and/or resolved effusion, as confirmed by echocardiography. In another study, Varol et al. reported increased CA 125 levels in severe HF patients with pericardial effusion, compared to those with mild to moderate HF without pericardial effusion (9). The authors found that CA 125 was the most correlated with clinical presentation among all tumor biomarkers. However, no significant difference in medical treatment was observed. Another study including patients with mitral stenosis, the authors concluded that increased CA 125 levels were associated with increased signal peptides, peritoneal mesothelial cell activation, and venous congestion (17).

Furthermore, De Ganarro et al. assessed 47 patients with HF and reported that serum BNP levels were increased in patients with stage IV disease compared to others (18). Consistent with our results, CA 125 levels were increased in patients with stage III-IV disease than those with stage I-II.

In another study including 191 HF patients, Faggino et al. observed that only CA 125 among the other tumor biomarkers were associated with HF functional class with statistically significant decreased CA 125 levels with medical treatment (4). The authors also reported that symptomatic patients with significantly higher serum CA 125 levels had concomitantly increased serum BNP levels with a significant decrease with medical treatment. Another study including 286 patients, the authors observed increased CA 125 and BNP levels in patients with stage III-IV disease with a significant increase in stage IV, particularly. The authors showed increased BNP and CA 125 levels in the presence of reduced LVEF, suggesting an inverse relationship between LVEF and BNP and CA 125 levels (19,20). In addition, recently it was reported that serum CA 125

and BNP levels were significantly associated with cardiac mortality and prognosis (21, 22).

Moreover, Nagele et al. evaluated CA 125 levels in HF patients who were evaluable for heart transplantation (7). The authors demonstrated that these patients had markedly high serum CA 125 levels. The levels returned to normal after transplantation. Furthermore, D'Aloia et al. reported increased serum CA 125 levels in HF patients both with pleural, peritoneal, and pericardial effusion and advanced disease without effusion (19). The levels were reduced by clinical improvement.

Limitations of our study, lack of registration of pleural effusion in patients, the small number of patients and the lack of advanced statistical analysis.

In conclusion, our results showed that patients with stage III-IV HF had significantly higher CA 125 and pro-BNP levels compared to those with stage I-II disease. We suggest that, serum CA 125 and pro-BNP may be useful in the diagnosis and staging of HF.

Ethics Committee Approval: İzmir Tepecik Training and Research Hospital Local Ethics Committee permission was obtained with the letter dated 17.06.2009 and Decision number 11/VII.

References

1. Bates SE. Clinical applications of serum tumor markers. Ann Intern Med. 1991;115:623-38.
2. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. Adopted on May 17, 1996 by the American Society of Clinical Oncology. J Clin Oncol. 1996;14(10):2843-77.
3. Antony W. Burch, Nicole A. Massol, Alex A. Pappas. Tumor markers in Clinical Chemistry. Principles, procedures, correlations. Michael L. Bishop Janet L. Duben, Engel Kirk Edward P. Fody, Eds. Lippincott Williams and Wilkins, Phledelphia, USA, 4th ed. 2000:522-36.
4. Faggiano P, D'Aloia A, Brentana L, et al. Serum levels of different tumour markers in patients with cronic heart failure. Eur J Heart Fail. 2005;7(1):57-61.
5. Faggiano P, D'Aloia A, Bignotti T, Dei Cas L. One biologic marker (carbohydrate antigen-CA 125), two different disease (ovarian cancer and congestive heart failure): practical implications of monitoring CA 125 serum levels. A case report. Ital Heart J. 2003;4(7):497-9.
6. Hopman EH, Helmerhorst TJ, Bunfrer JM, Ten Bukkel Huinink WW. Highly elevated ± serum CA 125 levels in a patient with cardiac failure. Eur J Obstet Gynecol Reprod Biol. 1993;48:71-3.
7. Nagele H, Bahlu M, Klapdor R, Schaeperkoeter D, Rfdiger W. CA 125 and its relation to cardiac function. Am Heart J. 1999;137:1044-9.
8. Kouris N.T, Zcharos I. D,Kontogianni D. et al. The significance of CA 125 levels in patients with chronic congestive heart failure. Correlation with clinical and achocardiographic parameters. Eur J Heart Fail. 2005;7(2):199-203.
9. Varol E, Özaydın M, Doğan A, Kaşar F. Tumour marker levels in patients with chronic heart failure. Eur J Heart Fail. 2005;7(5):840-3.
10. Vizzardi E, D'Aloia A, Pezzali N, Bugatti S, Curnis A, Dei Cas L. Long-term prognostic value of CA 125 serum levels in mild to moderate heart failure patients. J Card Fail. 2012;18(1):68-73.
11. Karaca O, Guler GB, Guler E. et al. Serum carbohydrate antigen 125 levels in nonischemic dilated cardiomyopathy: a useful biomarker for prognosis and functional mitral regurgitation. Congest Heart Fail. 2012;18(3):144-50.
12. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440.
13. Lavin PT, Knapp RC, Malkasion G, Whitney CW, Berek JC, Bast Jr RC. CA 125 for the monitoring of ovarian carcinoma during primary therapy. Obstet Gynecol. 1987;69:223-7.
14. Seo T, Ikeda Y, Onaka H, et al. Usefulness of serum CA 125 measurement for monitoring pericardial effusion. Jpn Circ J. 1993;57(6):489-94.
15. Spann JF, Bove AA, Natarajan G, Kreulen T. Ventricular performance, pump function and compensatory mechanisms in patients with aortic stenosis. Circulation. 1990;82:2075-82.
16. Zacharos ID, Efstathiou SP, Petreli E, Georgiou G, Tsioulos DI, Mastorantonakis SE, Christakopoulou I, Rousou PP. The prognostic significance of CA 125 in patients with non-Hodgkin's lymphoma. Eur J Haematol. 2002;69(4):221-6.
17. Duman C, Ercan E, Tengiz I, Bozdemir H, Ercan HE, Nalbantgil I. Elevated serum CA 125 levels in mitral stenotic patients with heart failure. Cardiology. 2003;100(1):7-10.
18. De Gennaro L, Brunetti ND, Bungara R, et al. CA-125:additional accuray in identifing patients at risk of acute heart failure in acute coronary syndrome. Coron Artery Dis. 2009;20(4):274-80.
19. D'Aloia A, Faggiano P, Aurigemma GP, et al. Serum levels of carbohydrate antigen 125 (CA 125) in patients with chronic heart failure. Relation with clinical severity, hemodynamic and Doppler echocardiographic abnormalities and short term prognosis. J Am Coll Cardiol. 2003;41(10):1805-11.
20. Zhuang J, Faggiano P, Li Q, et al. Insights into the clinical implications of carbohydrate antigen 125 as a biomarker of heart failure: a meta-analysis and systematic review of published studies. J Cardiovasc Med (Hagerstown). 2014;15(12):864-72.
21. Folga A, Filipiak KJ, Mamcarz A, Obrebska-Tabaczka E, Opolski G. Simultaneous predictive value of NT-proBNP and CA-125 in patients newly diagnosed with advanced heart failure: preliminary results. Arch Med Sci. 2012;8(4):637-43.
22. Núñez J, Merlos P, Fácila L, et al. CHANCE-HF Investigators. Prognostic effect of carbohydrate antigen 125-guided therapy in patients recently discharged for acute heart failure (CHANCE-HF). Study design. Rev Esp Cardiol (Engl Ed). 2015;68(2):121-8.