Increased ultrasensitive C-reactive protein is not associated with obesity in hospitalized heart failure patients

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ABSTRACT

Objective: To evaluate the association between obesity and levels of high-sensitivity C-reactive protein (hs-CRP) in patients with heart failure admitted to a tertiary hospital. Methods: Cross-sectional study with a consecutive sampling of hospitalized patients with heart failure. Sociodemographic and clinical data were collected, and the nutritional status was assessed through indicators such as body mass index (in kg/m²), waist circumference (in cm), waist-hip ratio, triceps skinfold (in mm) and subscapularis skinfold (in mm). Neck circumference (in cm) was measured as well as serum levels of hs-CRP, in mg/L. Results: Among 123 patients, the mean age was 61.9±12.3 years and 60.2% were male. The median of hs-CRP was 8.87mg/L (3.34 to 20.01). A tendency to an inverse correlation between neck circumference and hs-CRP was detected (r=-0.167; p=0.069). In the multiple linear regression analysis, after adjustment for age, disease severity (NYHA classification III and IV, low ejection fraction, left ventricular dysfunction during diastole), and infectious conditions there was an inverse association between hs-CRP and neck circumference (ß=-0.196; p=0.03) and subscapularis skinfold (ß=-0.005; p=0.01) in the total sample, which was not maintained after the stratification by sex. Conclusion: Increased levels of hs-CRP in patients hospitalized for heart failure were not associated with obesity.

Keywords: Heart failure; Obesity; C-reactive protein

INTRODUCTION

Heart failure (HF) is characterized as a highly complex syndrome due to the structural and functional alterations of the heart, involving several causal and compensatory mechanisms.[1] This is a condition considered endemic
in developing countries, such as Brazil, and it is a frequent cause of death and admissions to hospital. (2)

Among the possible factors associated with the genesis of HF, obesity stands out. (3) Nevertheless, it is suggested that patients diagnosed with HF and with excess weight have greater survival when compared to normal-weight patients diagnosed with the disease, as per the body mass index (BMI). (4) The adipose tissue, present in an excessive amount in obese individuals, is an endocrine organ, which is involved in the regulation of physiological and pathological mechanisms (including inflammatory processes), (5) in which acute phase protein concentrations, as well as that of pro-inflammatory cytokines, are elevated. (6)

C-reactive protein CRP is an amply studied acute phase inflammatory mediator of cardiovascular diseases (7) and is considered an unspecific marker of systemic inflammation. (8) High-sensitivity CRP (hs-CRP) has prognostic value for ischemic cardiopathy and HF. (9,10) High levels of hs-CRP in patients with HF are associated with increased morbidity and mortality in cases of ischemic and non-ischemic etiology. (11)

Both neurohumoral and inflammatory activations are considered important mechanisms for the progression of HF. Patients with HF and high levels of hs-CRP were twice as likely to be readmitted to hospital and die, when compared to individuals with lower levels of hs-CRP. (11)

**OBJECTIVE**

To evaluate the association between central and general obesity indicators and levels of high-sensitivity C-reactive protein among patients with heart failure admitted to a tertiary care hospital.

**METHODS**

This is a cross-sectional analysis of the baseline of a cohort study which consecutively enrolled patients admitted due to HF at the Cardiology Service of the Hospital Nossa Senhora da Conceição (HNSC) in the city of Porto Alegre (RS).

The inclusion criteria were New York Heart Association (NYHA) class I-IV history of HF; (12) systolic and diastolic HF; age between 20 and 85 years; absence of history or clinical evidence of severe complications related to HF over the previous 30 days; patients who resided in the metropolitan region of Porto Alegre, and who agreed to participate in the study. The exclusion criteria were situations that precluded anthropometric evaluation (amputation of limbs or sequelae from a stroke), and unwillingness to participate in the study.

The initial clinical evaluation was done by physicians and medical students trained and with the supervision of cardiologists. Training was given during the pilot study, in which the students applied the questionnaire to hospitalized patients, with characteristics similar to those who were, in fact, enrolled in the study.

The variables studied consisted of clinical and sociodemographic data and issues relative to smoking and alcohol consumption, besides anthropometric evaluations done by equally trained dieticians and nutrition students. Associated morbidities were identified from the patient’s past history; prior medical diagnoses were recorded: type 2 diabetes mellitus, systemic arterial hypertension, chronic renal failure, anemia, and dyslipidemia.

Data on inflammatory conditions among the patients were collected by a physician from the organization, considering the following inflammatory diseases: chronic obstructive pulmonary disease exacerbated during hospitalization, pneumonia, rheumatic diseases, autoimmune diseases, urinary tract disease, and sepsis. The levels of hs-CRP were evaluated according to the protocol of the HNSC clinical analyses laboratory, based on the nephelometry method. (13)

Weight was checked by means of a digital scale, with the patient wearing light clothing and no shoes. In cases of volemic alterations confirmed by means of a physical examination (presence of edema), the patient’s weight was verified after treatment for this condition, and if there was residual edema, a formula for an estimate of body weight adjusted for edema was used. (14) Height was checked with the help of a fixed stadiometer and the BMI was calculated; for classification of overweight and obese, the cutoff points were ≥25kg/m² and ≥30kg/m², respectively. (15)

With an inelastic tape measure, the following measurements in centimeters were made: waist circumference (WC), considering the minimum circumference between the ribs and the pelvis; hip circumference (HC), with the maximum circumference in the hip region; and neck circumference (NC), at the midpoint of the neck. Abdominal obesity was defined as a value of WC ≥102cm for men and ≥88cm for women, (16) and the waist-hip ratio (WHR) >0.95 for men and >0.85 for women. (17)

Checking of the tricipital skin fold (TSF) was done with the patient standing or sitting, with the non-dominant arm freely extended along the body; the
The skin folds were identified by means of an adipometer.

HF etiology was defined by the cardiologist and collected in the patient medical record (secondary data). The patients underwent transthoracic echocardiography with color Doppler, and measures of systolic function and calculation of the ejection fraction (EF) were made using Teichholz formula;\(^{(19)}\) individuals with segment alterations in left ventricle contractility had their EF determined by Simpson method. All patients did the stress test on a treadmill with a slope protocol.\(^{(20)}\)

The study was approved by the Research Ethics Committees of the HNSC, under protocol 10-118, of August 2010, and of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSA), under protocol 1,747, of June 2012. All individuals participating in the study signed the Informed Consent Form.

The sample size was calculated by means of the WinPepi program, version 11.15. Considering a prevalence of obesity of 30% among patients with HF (ratio of 2:1), a prevalence of elevated hs-CRP of 60% among obese (exposed), and of 30% among the non-obese, the size of the sample was estimated as at least 96 patients, for a 95% confidence level and 80% power.\(^{(21,22)}\)

The statistical analysis was made using the Statistical Package for the Social Sciences (SPSS), version 22.0. Continuous variables were described by means and standard deviation when they showed a symmetric distribution, and by medians and interquartile interval in asymmetric distributions. To evaluate the difference in the continuous symmetric variables, Student’s \(t\) test was used; for asymmetric variables, Mann-Whitney’s test was employed; and for categorical variables, Fisher’s exact test. To evaluate correlations, Pearson’s correlation was used, and to adjust confounding variables, multiple linear regression was employed. In all analyses, a 5% level of significance was considered.

**RESULTS**

A total of 123 inpatients were evaluated predominantly presenting acute decompensation of HF, with a mean age of 61.9±12.3 years, 60.2% males, and 84.3% of them classified as NYHA functional classes III and IV. Table 1 presents the general characteristics of the sample.

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**Table 1. General characteristic of the population**

| Variable                        | Total (n=123) | Male (n=74) | Female (n=49) | p value |
|---------------------------------|---------------|-------------|---------------|---------|
| Age (years)                     | 61.97±12.29   | 61.30±11.62 | 62.98±13.29   | 0.46\(^*\) |
| **Self-referred ethnicity**     |               |             |               |         |
| White                           | 89 (72.4)     | 53 (71.6)   | 36 (73.5)     | 0.25\(^t\) |
| Mixed/Mulatto                   | 16 (13)       | 7 (9.5)     | 9 (18.4)      |         |
| Black                           | 13 (10.6)     | 10 (13.5)   | 3 (6.1)       |         |
| Other                           | 5 (4)         | 4 (2.6)     | 1 (2)         |         |
| **Smoking**                     |               |             |               |         |
| Smoker                          | 15 (12.3)     | 11 (15.1)   | 4 (8.2)       | 0.16\(^t\) |
| Former smoker                   | 59 (48.4)     | 38 (52.1)   | 21 (42.9)     |         |
| Never smoked                    | 48 (39.3)     | 24 (32.9)   | 24 (49)       |         |
| **NYHA functional class**       |               |             |               |         |
| I                               | 2 (1.7)       | 1 (1.4)     | 1 (2)         | 0.23\(^t\) |
| II                              | 17 (14)       | 9 (6.6)     | 10 (20.8)     |         |
| III                             | 66 (54.5)     | 44 (60.3)   | 22 (45.8)     |         |
| IV                              | 36 (29.8)     | 21 (28.7)   | 15 (31.3)     |         |
| **EF (%)**                      | 39.92±14.45   | 36.45±13.44 | 45.19±14.46   | 0.001\(^*\) |
| **HF etiology**                 |               |             |               |         |
| SAH                             | 97 (79.5)     | 54 (73)     | 43 (89.6)     | 0.38\(^t\) |
| Cardiomyopathy                  | 39 (31.7)     | 29 (39.2)   | 10 (20.4)     |         |
| Ischemic disease                | 29 (23.6)     | 18 (24.3)   | 11 (22.4)     |         |
| Other                           | 13 (10.5)     | 8 (10.8)    | 5 (10.2)      |         |
| **Associated morbidities**      |               |             |               |         |
| SAH                             | 97 (79.5)     | 54 (73)     | 43 (89.6)     | 0.38\(^t\) |
| Dyslipidemia                    | 45 (36.9)     | 25 (33.8)   | 20 (41.7)     | 0.44\(^t\) |
| DM2                             | 42 (34.4)     | 23 (31.1)   | 19 (39.6)     | 0.43\(^t\) |
| CRF                             | 25 (20.5)     | 14 (16.9)   | 11 (22.9)     | 0.64\(^t\) |
| Anemia                          | 21 (17.2)     | 4 (5.4)     | 17 (35.4)     | <0.001\(^t\) |
| **Blood pressure**              |               |             |               |         |
| SBP (mm/Hg)                     | 122.66±18.55  | 120.89±18.64| 125.39±18.26  | 0.20\(^*\) |
| DBP (mm/Hg)                     | 75.38±11.49   | 74.58±11.78 | 76.61±11.04   | 0.35\(^t\) |
| hs-CRP (mg/L)\(^\dagger\)       | 8.87 (0.79-180)| 11 (0.8-101)| 7.80 (0.9-180)| 0.23\(^\dagger\) |

* Categorical variables expressed in n (%) and continuous variables as mean ± standard deviation or median (interquartile interval). \(^*\) Student’s \(t\) test; \(^t\) Fisher’s exact test; \(^\dagger\) Evaluated in 119 individuals; \(^\ddagger\) Mann-Whitney’s test; \(^\ddagger\) Evaluated in 121 individuals.

As to associated morbidities, 79.5% of patients presented with a past history of systemic arterial hypertension, 36.9% of dyslipidemia, 32% of type 2 diabetes mellitus, 20.5% of chronic renal failure, and 17.2% of anemia. There was no significant difference between the morbidities according to sex, with exception of the prevalence of anemia, statistically higher among women (35.4% versus 5.4%; \(p<0.001\)). The mean EF was 39.9±14.5%, and women showed a higher EF compared to men: 45.2±14.5% and 36.5±13.4%, respectively (\(p=0.001\)).
Thirty-four individuals were identified (28.5%) with some type of infection concomitant with HF during hospitalization. Figure 1 shows the percentage of individuals identified in each clinical picture according to sex, and there was no significant difference between men and women.

The mean BMI was 28.5±6.5kg/m², with a prevalence of excess weight in the sample of 64.2%. Obesity was more frequent in women (46.9%), and overweight in men (39.2%). Table 2 displays the classifications of obesity and overweight according to different criteria of anthropometric evaluation per sex.

For hs-CRP analyses, data in reference to 119 patients were used due to baseline losses, because the patient was discharged from the hospital before the test was requested. The median hs-CRP in the sample was 8.87mg/L (3.34 a 20.01), and table 3 represents the distribution of the nutritional status identified by different criteria, as per the hs-CRP tertiles.

No statistically significant correlations were noted between hs-CRP levels and weight (r=-0.031; p=0.74), BMI (r=0.44; p=0.63), WC (r=-0.04; p=0.67), TSF (r=0.31; p=0.74), and SSF (r=0.02; p=0.86). However, a tendency was detected towards an inverse correlation between NC and hs-CRP (r=-0.167; p=0.069).

Multiple linear regression analysis, adjusted for age, severity of disease (NYHA classification III and IV, low EF, HF with preserved EF), and presence of infection indicated an inverse association relative to hs-CRP and NC (β=-0.196; p=0.03) and PCS (β=-0.005; p=0.01). However, after stratification for sex, only the tendency towards association for NC was maintained both in men (β=-0.23; p=0.07) and in women (β=-0.27; p=0.08) (Table 4).
DISCUSSION
The evidence of a linear relation between obesity and hs-CRP found in healthy people does not seem to occur in HF patients. In our analysis, on the contrary, there was an inverse association between some anthropometric variables and hs-CRP levels.

Obesity is a condition of chronic inflammation, mediated by an increased production of cytokines and hs-CRP by adipocytes.(23) There is an association between hs-CRP and the anthropometric indicators in patients with no history of HF.(24-26) Sanip et al., in a study with 91 healthy postmenopausal women, found a correlation between hs-CRP and obesity, highlighting BMI (r=0.281; p=0.007), WC (r=0.340; p=0.001), and HC (r=0.257; p=0.014).(24)

In our study, it was possible to observe high levels of hs-CRP, a fact that likely can be explained by severity of disease, exacerbation of HF symptoms, or presence of comorbidities that led the patients to hospitalization. The high level of hs-CRP found corroborates the findings of Chen et al., in which patients evaluated during hospital admission presented with mean hs-CRP of 53±57.7mg/L.(27) On the other hand, among Japanese assessed as outpatients (mean hs-CRP of 10.9±18mg/L as baseline), the individuals classified in the largest quartile of hs-CRP (>11mg/L) had the worst prognosis after three years.(28)

The sample distribution was homogeneous relative to sex; 60.2% of individuals were men, thus allowing extrapolation of results in a more significant manner for both sexes. These findings were different from those of most observational studies, which address the paradox of obesity, when the difference between sexes tends towards an absolute majority of men.(29,30)

Most of the sample was classified as severe, as per the NYHA functional classification, differing from the results of a cohort carried out in Porto Alegre, in which only 17% of patients were in functional classes III and IV.(4) This difference can be justified by the site of data collection, that is, the present study was performed during hospitalization, whereas the comparative cohort was carried out with outpatients, in whom likely patients of less gravity are seen.

The mean EF identified was similar to that found in other studies.(27,31) Galvao et al. identified differences between sexes as to EF similarly to our findings, in the study analysis from the Acute Decompensated Heart Failure National Registry (ADHERE).(32) considering that these differences can be justified by the better prognosis that women showed in HF progression compared to men.

In our study, we identified a prevalence of excess weight evaluated by means of a BMI of 64.2%, in which 30.9% were overweight and 33.3% were obese. Clark et al. described that, among individuals with HF, the prevalence of overweight varies between 31 and 40%, and from 32 to 49% for obesity.(29) These data corroborate those of other studies, displaying a similar prevalence of overweight and obesity.(33,36)

The mean NC identified was similar to that observed in another study conducted among individuals with HF and sleep apnea,(37) and the mean TSF was superior to that observed in outpatients.(4) As to the prevalence of overweight and obesity classified according to TSF, the present study identified 4.9% and 60.2%, respectively; Casas-Vara et al. found similar data relative to overweight, but great discrepancy in the prevalence of obesity (14.2% according to this classification criterion).33 As to SSF, we identified means similar to those of other authors.(38)

There are few studies evaluating the association of anthropometric measurements and the inflammatory profile of HF patients. In patients hospitalized for HF and evaluated in our study, the excess weight did not lead to increased hs-CRP. It is possible that the increase in weight be a benefit to these individuals, due to greater energy reserve, contrary to cardiac cachexia.(39) Another hypothesis is that HF causes ischemia and intestinal edema, allowing bacterial translocation and favoring the formation of endotoxins, contributing to an inflammatory state in individuals with HF, regardless of the degree of excess weight, favoring the loss of muscle mass, but not necessarily of fat mass.(40)

Some limitations must be considered: the study design (cross-sectional), which does not allow a definition of causality; and the sample size hindered the subgroup analysis. Another point to be highlighted refers to severity of patients enrolled for the sample: one cannot discard the fact that there is an association between hs-CRP and obesity in individuals with milder degrees of HF, making it difficult to generalize our results for patients with HF and less severe conditions. We also point out that, in the mathematical formula for estimating body weight adjusted for edema, despite being amply used in clinical practice, a relatively subjective approach is used. Additionally, the techniques used to identify skinfolds by means of adipometer do not have the same accuracy of the imaging methods to identify the body composition; and in cases of residual edema that is still present, these folds might have been overestimated.
CONCLUSION
In patients hospitalized due to heart failure, there is a significant increase in high-sensitivity C-reactive protein, but no association was found with obesity. Although obesity contributes towards high concentrations of high-sensitivity C-reactive protein in individuals with normal heart function, the exacerbated inflammatory state observed in severe cardiac failure seems to be a factor that influences these concentrations more significantly. Other studies that evaluate the prognostic impact of high-sensitivity C-reactive protein according to the nutritional status should be conducted to better utilize inflammatory markers in heart failure patients.

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REFERENCES
1. Bocchi EA, Arias A, Verdejo H, Díez M, Gómez E, Castro P; Interamerican Society of Cardiology. The reality of heart failure in Latin America. J Am Coll Cardiol. 2013;62(11):949-58. Review.
2. Braunwald E. Heart failure. JACC Heart Fail. 2013;1(1):1-20. Review.
3. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and risk of heart failure. N Engl J Med. 2002;347(5):305-13.
4. Zuchinali P, Souza GC, Alves FD, d’Almeida KS, Goldraich LA, Clausell NO, et al. Interamerican Society of Cardiology. III Diretrizes da Sociedade Brasileira de Cardiologia Sobre Teste Ergométrico. Arq Bras Cardiol. 2013;101(5):434-41.
5. Unek IT, Bayraktar F, Solmaz D, Ellidokuz H, Sisman AR, Yuksel F, et al. Prognostic value of hs-CRP in outpatients with heart failure. Am Heart J. 2007;153(6):1048-55. Review.
6. Piché ME, Lermieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. Am J Cardiol. 2005;96(1):92-7.
7. Hamer M, Chida Y, Stamatakis E. Association of very highly elevated C-reactive protein concentration with cardiovascular events and all-cause mortality. Clin Chem. 2010;56(1):132-5.
8. Tillette WS, Francis T. Serological reactions in pneumonia wiyh a non-protein somatic fraction of pneumococcus. J Exp Med. 1930;52(4):561-71.
9. Morrow DA, Rifai N, Antman EM, Weinier DL, McCabe CH, Cannon CP, et al. Prognostic value of C-reactive protein in heart failure. Arch Intern Med. 2002;162(17):2031-8.
10. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J. 2007;153(6):1048-55.
11. Araújo JP, Lourenço P, Azevedo A, Freões F, Rocha-Gonçalves F, Ferreira A, et al. Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. J Card Fail. 2009;15(3):256-66. Review.
12. American Heart Association. New York Heart Association (NYHA). Classes of Heart Failure [Internet]. Dallas: 2015 [cited 2016 July 14]. Available from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp
13. López-Campos JL, Arellano E, Calero C, Delgado A, Márquez E, Cejudo F, et al. Determination of inflammatory biomarkers in patients with COPD: a comparison of different assays. BMC Med Res Methodol. 2012;12:40.
14. Chumlea WC, Guo S, Roche AF, Steinbaugh ML. Prediction of body weight for the nonambulatory elderly from anthropometry. J Am Diet Assoc. 1988;88(5):564-8.
15. World Health Organization (WHO). Global Database on Body Mass Index. BMI Classification [Internet]. Geneva: WHO; 2004 [cited 2016 July 14]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
16. Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Cardiología; Sociedade Brasileira de Endocrinologia e Metabología; Sociedade Brasileira de Diabetes; Associação Brasileira para Estudos da Obesidade. I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica. Arq Bras Cardiol. 2005;84:3-28.
17. Sociedade Brasileira de Cardiología; Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Nefrologia. V Diretrizes Brasileiras de Hipertensão Arterial. Rev Bras Hipertens. 2006;13(4):256-312.
18. Waitzberg DL, Ferrini M. Exame físico e antropometria. Nutrição oral, enteral e parenteral na prática clínica. 4a ed. São Paulo: Atheneu; 2000.
19. Lang RM, Bleier M, Devereux RB, Flachskaempf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spence HT, Sutton MS, Stewart WU; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. 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(12):1440-63.
20. Sociedade Brasileira de Cardiología. III Diretrizes da Sociedade Brasileira de Cardiología Sobre Teste Ergométrico. Arq Bras Cardiol. 2010;95(5 suppl.1):1-26.
21. Pinheiro AS, Nakasato M, Iossaki M, Bocchi EA. Obesidade: fator protetor nos pacientes com insuficiência cardíaca? Rev Bras Nutr Clin. 2007;22(1):20-7.
22. Oreopoulos A, Ezekowitz JA, McAlister FA, Kalantar-Zadeh K, Fonarow GC, Norris CM, et al. Association between direct measures of body composition and prognostic factors in chronic heart failure. Mayo Clin Proc. 2010;85(7):809-17.
23. Baislisteri CR, Caruso C, Candelore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. Mediators Inflamm. 2010;2010:802078. Review.
24. Sanip Z, Ariffin A, Al-Tahami BA, Sulaiman WA, Rassol AH. Obesity indices and metabolic markers are related to hs-CRP and adiponectin levels in overweight and obese females. Obes Res Clin Pract. 2007;12(21):207-10.
25. Marques-Vidal P, Bochud M, Bastardot F, Lüscher T, Ferrero F, Gaspoz JM, et al. Association between inflammatory and obesity markers in a Swiss population-based sample (CoLaus Study). Obes Facts. 2012;5(5):734-44.
26. Oliveira A, Lopes C, Severo M, Rodrigo-Artalejo F, Barros H. Body fat distribution and C-reactive protein—an principal component analysis. Nutr Metab Cardiovasc Dis. 2011;21(5):347-54.
27. Chen CW, Lee YH, Chen HM, Lin YL. High-sensitivity C-reactive protein and other factors as outcome predictors in acute decompensated heart failure. Tzu Chi Med J. 2009;21(4):293-301.
28. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J. 2007;153(6):1048-55.
29. Clark AL, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. Prog Cardiovasc Dis. 2014;56(4):409-14. Review.
30. Melendez V, Kotrc M, Borlaug BA, Marek T, Kvarar J, Malek I, et al. Relationships between right ventricular function, body composition, and prognosis in advanced heart failure. J Am Coll Cardiol. 2013;62(10):1660-70.
31. Curtis JP, Sultzr FG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med. 2005;165(1):55-61. Erratum in: Arch Intern Med. 2008;168(6):567.
32. Galvao M, Kalman J, DeMarco T, Fonarow GC, Galvin C, Ghali JK, et al. Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Card Fail. 2006;12(2):100-7.

33. Casas-Vara A, Santolaria F, Fernández-Bereciartúa A, González-Reimers E, García-Ochoa A, Martínez-Riera A. The obesity paradox in elderly patients with heart failure: analysis of nutritional status. Nutrition. 2012;28(6):616-22.

34. Kapoor JR, Heidenreich PA. Obesity and survival in patients with heart failure and preserved systolic function: a U-shaped relationship. Am Heart J. 2010;159(1):75-80.

35. Gastelurrutia P, Lupón J, Domingo M, Ribas N, Noguero M, Martinez C, et al. Usefulness of body mass index to characterize nutritional status in patients with heart failure. Am J Cardiol. 2011;108(8):1166-70.

36. Clark AL, Chyu J, Horwich TB. The obesity paradox in men versus women with systolic heart failure. Am J Cardiol. 2012;110(1):77-82.

37. Alkatib S, Sankri-Tarbichi AG, Badr MS. The impact of obesity on cardiac dysfunction in patients with sleep-disordered breathing. Sleep Breath. 2014;18(1):137-42.

38. Nicol SM, Carroll DL, Homeyer CM, Zamagni CM. The identification of malnutrition in heart failure patients. Eur J Cardiovasc Nurs. 2002;1(2):139-47.

39. Waring ME, Saczynski JS, McManus D, Zacharias M, Lessard D, Gore JM, et al. Weight and mortality following heart failure hospitalization among diabetic patients. Am J Med. 2011;124(9):834-40.

40. Sandek A, Swidsinski A, Schroedl W, Watson A, Valentova M, Herrmann R, et al. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms, and cachexia. J Am Coll Cardiol. 2014;64(11):1092-102.