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The health outcomes of inflammation and obesity in patients with heart failure

Zyad T. Saleh, PhD^a, Terry A. Lennie, PhD, FAAN^b, Muhammad Darawad, PhD, RN^a, Hamza Alduraiddi, PhD, RN^a, Rami A. Elshatarat, PhD, RN^c, Issa M. Almansour, PhD, RN^a, Debra K. Moser, PhD, RN, FAAN^b

^aSchool of Nursing, The University of Jordan, Queen Rania Street, Amman, Jordan 11942

^bCollege of Nursing, University of Kentucky, 315 College of Nursing Building, 751 Rose Street, Lexington, KY 40536

^cDepartment of Medical and Surgical Nursing, College of Nursing, Taibah University, Madinah, Saudi Arabia 41477

Abstract

Background.—Although obesity is a risk factor for cardiovascular disease, higher body mass index is related to longer event-free survival in patients with heart failure (HF). While previous research demonstrated that higher levels of inflammatory mediators were associated with shorter event-free survival, the effect of inflammation on the association between obesity and outcomes of HF have not been considered.

Hypothesis.—Based on the obesity paradox, we hypothesized that patients with higher baseline body mass index (BMI) would experience better event-free survival than those with lower BMI regardless of inflammatory status.

Method.—A sample of 415 patients with HF (age 61±11.5 years; 31% female) provided blood to measure soluble tumor necrosis factor receptor1 (sTNFR1), a biomarker of inflammation. Patients were divided into 4 groups based on BMI and a median split of sTNFR1 levels: 1) high BMI ≥30 and sTNFR1>1804 pg/ml, 2) high BMI ≥30 and low sTNFR1 ≤1804 pg/ml, and 3) low BMI<30 and high sTNFR1>1804 pg/ml vs. 4) low BMI<30 and sTNFR1 ≤1804 pg/ml. Patients were followed for an average of 365 days to determine the time to first event of either all-cause hospitalization or death.

Results.—There were 177 patients (43%) who experienced either an all-cause hospitalization or death. In a Cox regression, high BMI and high sTNFR1 category predicted time to event (hazard ratio = 1.7, 95% confidence interval=1.01 – 2.9) with age, gender, race, left ventricular ejection

Corresponding Author: Zyad T. Saleh, PhD, Department of Clinical Nursing, School of Nursing, The University of Jordan, Amman, Jordan 11942. zyad.saleh2@ju.edu.jo, Tel: +962785358313, Fax: +96265300244.

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fraction, New York Heart Association functional class (I/II versus III/IV), log-transformed N-terminal Pro-B-type natriuretic peptide levels, prescribed statin(yes/no), and comorbidity as covariates.

Conclusion.—Being in a higher inflammation group was associated with shorter event-free survival regardless of BMI. This study provides evidence that inflammation is an important consideration in the association between obesity and better outcomes in patients with HF.

Keywords

Heart failure; inflammation; obesity; health outcome

Introduction

Obesity is a primary risk factor for cardiovascular disease and for other cardiovascular disease risk factors including hypertension, diabetes mellitus, and dyslipidemia.¹ The association of obesity and chronic subclinical inflammation is considered one of the major pathophysiologic mechanisms responsible for the development of cardiovascular disease in obese individuals.^{2,3} Subclinical inflammation in obesity is thought to be related to excretion of several pro inflammatory mediators including tumor necrosis factor- α (TNF- α).² Levels of pro inflammatory mediators are associated with the prognosis and severity of cardiovascular disease.^{3,4}

Subclinical inflammation is also a common feature of heart failure (HF).³ TNF- α and other pro inflammatory mediators are elevated in patients with HF independent of body mass index (BMI).^{3,5} Higher levels of these pro inflammatory mediators, particularly TNF- α , are associated with greater HF severity and worse HF prognosis.^{3,5} However, despite evidence linking obesity to chronic subclinical inflammation and cardiovascular disease, obesity in patients with HF has been paradoxically associated with better short- and long-term survival.⁶ One explanation is that obesity as a chronic inflammatory condition down regulates the immune system response to pro inflammatory conditions such as HF.^{2,6,7} Interestingly, the role of inflammation in the association between obesity and event-free survival in HF has not been considered. Therefore, we tested the hypothesis that patients with higher baseline BMI and higher inflammation would have similar event-free survival as those with lower baseline BMI and lower inflammation.

Methods

Design and Sample

Secondary data analysis was conducted using data from the RICH Heart Program databases.^{8–11} The sample included 415 patients with HF enrolled from 4 outpatient clinics located in Midwestern and Southeastern states for longitudinal observational studies. Only patients recruited for observational studies were included in this analysis. Enrolled patients were required to 1) understand and speak English, 2) have a diagnosis of HF with either reduced left ventricular ejection fraction (LVEF < 40%) or preserved ejection fraction confirmed by a cardiologist, and 3) have been on consistent dosing of HF medications during the same 3 month period. Patients were excluded if they had a BMI < 18.5 kg/m², were Status 1A or 1B

for heart transplantation, on immunosuppressant medications, experienced a myocardial infarction or were hospitalized in the 3 months before enrollment, had terminal illnesses such as end-stage lung or liver disease, or were enrolled in other studies that included an intervention. Eligibility was determined through medical record review and face-to-face interview by trained research nurses

Measurements of variables

Demographic.—Age, gender, marital status, and ethnicity were self-reported using a standardized form.

Comorbidity.—Comorbidity burden was defined as the total score of Charlson Comorbidity Index. The index assesses the presence of 19 comorbid conditions, each of which weighed on a scale ranged from 1 to 6. Total scores range from 1 to 34, with higher scores indicating a higher comorbidity burden. Reliability and validity have previously been demonstrated.^{12,13} Comorbidity burden was included as a covariate because comorbidity burden is associated with shorter event-free survival.¹⁴

New York Heart Association (NYHA) functional class.—NYHA functional class is a subjective indicator of HF severity. NYHA functional class was determined by a face-to-face structured interview. Patients were classified in one of four classes according to the severity of their HF symptoms. Due to insufficient numbers in several functional classes. The classes were collapse into two groups: I/II (less symptomatic) vs. III/IV (more symptomatic). Interrater and intrarater reliability for patients' classification were previously confirmed.^{10,15}

N-terminal pro-B-type natriuretic peptide (NT-proBNP).—NT-pro BNP is a hormone released by cardiomyocytes in response to increasing left intra-atrial or ventricular filling pressure. NT-pro BNP is increased in patients with HF¹⁶ with higher levels predictive of poor functional status and worse HF prognosis independent of BMI.^{17,18} NT-pro BNP levels were measured by enzyme-linked immunoassay kits (ELISA) (ALPCO Diagnostics). The accuracy and reproducibility of ELISA measurement of NT-pro BNP levels in our sample were demonstrated previously.¹⁰ Serum levels of NT-pro BNP were quantified in fmol/ml.

Soluble tumor necrosis factor receptor1 (sTNFR1).—Serum levels of sTNFR1 were used to indicate systemic TNF- α inflammatory activity.^{19–22} TNFR1 is a cell membrane protein receptor that is shed from cell membranes after binding with TNF- α . Increased serum sTNFR1 is an indicator of increased TNF- α activity.²² Serum levels of sTNFR1 were determined from blood drawn at baseline using ELISA kits (R&D Systems, Minneapolis, MN) as previously described.¹⁹ The ELISA method had a sensitivity of 3pg/ml and all duplicate samples had a coefficient of variation below 9%.¹⁹ Because there are no standardized normal values for sTNFR1, we used the median level of 1804 pg/ml as the cut point to categorize patients into either lower or higher inflammation groups. The median was chosen because sTNFR1 levels were positively skewed. Previous clinical studies used a similar method to determine whether sTNFR1 predicted HF prognosis.^{23–25}

Body mass index (BMI).—BMI was defined as the ratio of weight in kg to height in meters squared. Standardized measurement protocols were used to determine height using a professional grade stadiometer and weight using a professional grade digital scale.^{26,27} Weight was measured after confirming the absence of visible signs of fluid retention including ankle edema, jugular venous distention, and ascites.

Other clinical characteristics.—Data on prescribed medication therapy and LVEF were obtained by patient interview or medical record review.

Event-free survival.—Event-free survival was the number of days from the date of enrollment to the first event defined as a non-elective hospitalization for any cause or all-cause death during the follow-up period. Data on events were obtained by monthly telephone contact with patients or their family members and verified through medical record review or, in the case of death, by public death record review.

Procedure

This study was approved by the Institutional Review Board at each participating site. Patients were recruited during their regular clinic visits. Nurse practitioners or cardiologists at participating clinics referred patients to trained research nurses. The research nurses verified enrollment eligibility and provided eligible patients with full, detailed information about the study. Interested patients signed an informed consent prior to participation and completed a demographic questionnaire, Charlson Comorbidity Index, and a structured interview to determine NYHA functional class. At a follow up visit to the clinical research center, a research nurse drew venous blood samples for measurement of sTNFR1 and NT-proBNP levels. All samples were stored frozen at -80°C and preserved in dry ice during shipment to the main study site where the analysis of all blood samples took place. Research nurses contacted patients or their family members monthly to collect all-cause hospitalization or mortality data. Verification that the patient had not enrolled in a clinical trial or other intervention study was also obtained during the monthly follow up phone call.

Statistical Analysis

For the purpose of this study, we created 4 groups based on BMI and median split of sTNFR1 levels: 1) obese/high inflammation: BMI $\geq 30 \text{ kg/m}^2$ and sTNFR1 $> 1804 \text{ pg/ml}$; 2) obese/low inflammation: BMI $\geq 30 \text{ kg/m}^2$ and sTNFR1 $\leq 1804 \text{ pg/ml}$; 3) non-obese/high inflammation: BMI $< 30 \text{ kg/m}^2$ and sTNFR1 $> 1804 \text{ pg/ml}$; and 4) non-obese/low inflammation: BMI $< 30 \text{ kg/m}^2$ and sTNFR1 $\leq 1804 \text{ pg/ml}$. This approach is consistent with prior studies on the obesity paradox and allowed us to test our hypothesis and compare our findings with previous research.^{24,25,28}

All statistical analyses were conducted using SPSS software for Windows (version 25.0; IBM Corporation). Serum NT-pro-BNP levels were log-transformed due to non-normal distribution. Demographic and clinical characteristics among 4 groups were compared by one-way analysis of variance with least significant difference post hoc tests or χ^2 test of association. Cox regression was used to determine whether obesity/inflammation group predicted event-free survival controlling for covariates. Two models were tested. The first

model included age, gender, race, LVEF, NYHA functional class (I/II vs. III/IV), prescribed statin (yes/no), and comorbidity burden as covariates. The second model included the same covariates plus log transformed NT-proBNP levels. Hazard ratios with 95% confidence intervals are reported. The significance level was set at 0.05 a priori.

Results

Patient characteristics

The characteristics of the 415 patients included in the study are reported in Table 1. A greater proportion of patients were male, white, and married or cohabitating. Approximately half were obese, in NYHA functional class III or IV, with a mean LVEF of 34.9 ($\pm$ 14.4), comorbidity score of 3 ($\pm$ 1.9), and median NT-pro BNP levels of 712 (25th, 75th quartile; 347 – 884 fmol/ml).

The obese/low inflammation group was younger and with a greater proportion of black or other minority while non-obese/high inflammation group was older than all the other groups and with a greater proportion of Caucasians. Patients in the high inflammation groups were older and had higher comorbidity scores and NT-pro BNP levels than those in the low inflammation groups. The obese/high inflammation group had a higher BMI and a greater number in NYHA class III/IV than all other groups.

Obesity and event-free survival in the context of inflammation status

Table 2 shows a comparison of events among patients classified by BMI and inflammation status. There were 177 events, consisting of 10 deaths (5.7%) and 167 hospitalizations (94.3%) during a median follow-up of 365 days (25th, 75th quartile; 185 – 431 days). Patients in the high inflammation groups had greater number of events of all-cause hospitalization or death and shorter median time to first event free-survival than those in the low inflammation groups. The obese/high inflammation group had greater number of hospitalizations with HF as secondary diagnosis while non-obese/high inflammation group had higher rates of all-cause death than all other groups.

The first Cox regression model was significant (Omnibus test of model coefficients; $\chi^2 = 30.8$, $p = 0.001$). Both the obese/high inflammation and non-obese/high inflammation groups had nearly a 1.7 times higher risk for an event than the non-obese/low inflammation group controlling for age, gender, race, comorbidity score, NYHA functional class, LVEF, and prescribed statin (Figure 1). There was no difference in event-free survival between obese and non-obese low inflammation groups.

The second Cox regression model with the addition of log-transformed NT-pro BNP levels (Table 3) was significant (Omnibus test of model coefficients; $\chi^2 = 45.3$, $p < 0.0001$). The risk of an event for the obese/high inflammation group was minimally decreased (0.5%) and remained significant. In contrast, the risk of an event in the non-obese/high inflammation group was no longer significant (Figure 2).

Discussion

Our hypothesis was not supported. Results from previous studies suggested that obesity in patients with HF was paradoxically associated with better short- and long-term survival.^{6,24,25,28,29} Conversely, this study demonstrated that obesity in patients with HF was not associated with better survival when inflammatory status was considered. Prior studies of the relationship between BMI and survival did not consider inflammatory status even though it is common in obesity and contributes to poor prognosis in HF. Our study adds to the literature by providing evidence that inflammation changes the relationship between obesity and event-free survival in patients with HF.

Inflammatory markers were highest among obese patients with the highest BMIs, which was the group with the shortest event-free survival. This is consistent with previous findings of that level of inflammation is related to BMI.³⁰ Several investigators have reported an inverse relationship between BMI and event-free survival among obese individuals after controlling for multiple demographic and clinical variables.^{31,32} As above, our results suggest that inflammation is a potential mechanism to explain why greater BMI was associated with worse outcomes in those patients with HF.

NT-pro BNP levels were the strongest independent predictor of event-free survival in the second model. In that model, being in the non-obese/higher inflammation group no longer predicted event-free survival while being in the obese/high inflammation group remained a predictor. Several observations may explain this finding. First, NT-pro BNP levels were higher in the non-obese/higher inflammation group than in all other groups including the obese/higher inflammation group. Second, obese patients with heart failure are known to have lower NT-pro BNP levels compared with non-obese patients.^{33,34} This suggests that obesity was the factor related to lower NT-pro BNP levels in the obese/high inflammation group and inflammation was the factor related to the higher NT-pro BNP levels in the non-obese/high inflammation group. Consequently, in the second model inflammation likely played the major role in predicting event-free survival in the obese/high inflammation group and NT-pro BNP played the major role in predicting event-free survival in the non-obese/high inflammation group. Additional research is needed to verify this conclusion.

Our study had limitations. This was an observational study, consequently, causal inferences cannot be drawn. Our sample was categorized into 4 groups by BMI and sTNFR1 level to allow comparison with other studies. Although not the purpose of the study, this approach did not allow us to test whether BMI and inflammation were independent predictors of event-free survival. Future longitudinal studies are needed to clarify their independent contribution to survival. Body weight and inflammation were only measured at baseline. It is possible that some patients developed cardiac cachexia or experienced a change in inflammatory status over time.³⁵ However, BMI at baseline has been demonstrated to be a predictor of event-free survival in large clinical trials suggesting baseline BMI is a valid predictor of long-term survival.²⁵ Similarly, baseline measures of sTNFR1 have also previously been shown to predict long-term survival.³⁶ Finally, although there was a difference in racial make-up of the obese/low inflammation group compared with the other groups, race was not a predictor of event-free survival. This may be due to an under-

representation of minorities in our sample. Thus, caution should be used in generalizing these results to patients other than non-Hispanic white.

Conclusion

Contrary to our hypothesis, obese patients with HF and higher inflammation had shorter event-free survival than non-obese patients with lower inflammation when other important covariates were included in predictive models. Prior studies of the obesity paradox did not consider inflammation in their models. Thus, these results provide further clarification of the obesity paradox by considering the role of inflammation in the risk for an event among obese and non-obese patients with HF. Clinicians should be aware that a subpopulation of obese patients with HF who have higher inflammation may be at greater risk of hospitalization or death than other patients with HF.

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HIGHLIGHTS

- Higher inflammation was associated with shorter event-free survival, regardless of body mass index.
- Inflammation plays an important role in modifying the association between obesity and better outcomes in patients with heart failure.
- Obesity does not have a protective role with respect to inflammation in patients with heart failure.

Figure 1.

Cox regression for time to all-cause hospitalization or death in patients divided by body mass index and inflammation status

Figure 2.

Cox regression for time to all-cause hospitalization or death after controlling for NT-proBNP in patients divided by body mass index and inflammation status

Table 1

Sample characteristics and between-group comparisons based on BMI and inflammation status

Characteristics	Total sample (n = 415)	Obese/high inflammation (n = 118)	Obese/low inflammation (n =106)	Non-obese/high inflammation (n = 93)	Non-obese/low inflammation (n = 98)
Age	60.7 ± 11.5	60.8 ± 9.7	55.2 ± 11.7 ^a	66.9 ± 10.8 ^a	60.6 ± 10.9
Gender (male)	286 (68.9)	74 (77.6)	72 (68.8)	64 (68.8)	76 (77.6)
Race					
White	323 (77.8)	91 (77.1)	67 (63.2)	84 (90.3) ^a	81 (82.7)
Black or other minority	92 (22.2)	27 (22.9)	39 (36.8) ^a	9 (9.7)	17 (17.3)
Married or cohabitate	235 (56.7)	59 (50.0)	56 (52.8)	56 (60.2)	64 (65.3)
BMI (kg/m ²)	31.6 ± 7.4	37.5 ± 6.5 ^a	36.0 ± 4.9	25.4 ± 2.9	25.6 ± 3.2
LVEF (%)	34.9 ± 14.4	38.3 ± 15.4 ^b	35.8 ± 13.4 ^b	30.9 ± 13.7	33.9 ± 13.8
NYHA (III/IV)	195 (47.0)	75 (63.6) ^a	43 (40.6)	43 (46.2)	34 (34.7)
ACEI	289 (69.6)	80 (67.8)	77 (72.6)	59 (63.4)	73 (74.5)
ARB	72 (17.4)	20 (17.0)	22 (20.8)	16 (17.2)	14 (14.3)
Digoxin	102 (24.6)	21 (17.8)	26 (24.5)	32 (34.4) ^a	23 (23.5)
Diuretics	300 (72.3)	99 (83.9)	79 (74.5)	66 (70.9)	56 (57.1) ^a
β-blocker	363 (87.5)	105 (89.0)	90 (84.9)	79 (85.0)	89 (90.8)
Nitrates	72 (17.4)	21 (17.8)	18 (17.0)	21 (22.6)	12 (12.3)
Aldosterone antagonist	97 (23.4)	35 (29.7)	20 (18.9)	24 (25.8)	18 (18.4)
Calcium channel blocker	53 (12.8)	12 (10.2)	14 (13.2)	12 (12.9)	15 (15.3)
Anti-dyslipidemia	285 (68.7)	77 (65.3)	71 (67.0)	61 (65.6)	76 (77.6)
Aspirin	240 (57.8)	66 (55.9)	54 (50.9)	62 (66.7)	58 (59.2)
Comorbidity score	3.0 ± 1.9	3.6 ± 2.1 ^c	2.7 ± 1.8	3.2 ± 2.0 ^c	2.2 ± 1.2
NT-proBNP (fmol/ml)	711.6 ± 551.3	712.0 ± 537.4	510.7 ± 265.2 ^a	946.2 ± 717.1 ^a	691.1 ± 526.1
sTNFR1 (pg/ml)	2049.6 ± 1014.4	2644.7 ± 878.2	1418.0 ± 238.2	2758.6 ± 1250.3	1343.5 ± 255.8

Values are mean ± SD or frequency (percent).

sTNFR1: soluble tumor necrosis factor receptor1; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association functional class; LVEF: left ventricular ejection fraction; BMI: body mass index; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

P < .05

^a versus all the other groups;^b versus the non-obese groups;^c versus the low inflammation groups

Table 2

Event-rates and median time to first event for the total sample and patients groups classified based on BMI and inflammation status

	Total sample (n = 415)	Obese/high inflammation (n = 118)	Obese/low inflammation (n =106)	Non-obese/high inflammation (n = 93)	Non-obese/low inflammation (n = 98)
Events (total)	177 (42.7)	60 (50.9) ^b	40 (37.7)	44 (47.3) ^b	33 (33.7)
Death	10 (5.7)	2(3.3)	1 (2.5)	6 (13.6) ^a	1 (3.0)
Hospitalization					
cardiac	97 (54.8)	27 (45.0)	24 (60.0)	24 (54.6)	22 (66.7)
other	70 (39.6)	31 (51.7) ^a	15 (37.5)	14 (31.8)	10 (30.3)
Median time to first event (days)	185 (79, 361)	161 (50, 372) ^b	203 (105, 418)	175 (66, 322) ^b	195 (108, 336)

Values are n (%) or median (25th, 75th quartile)

P < .05

^a versus all the other groups;

^b versus the low inflammation groups

Table 3

Cox proportional hazards regression models for time to all-cause hospitalization or death

Variable	Adjusted hazard ratio	95% CI	<i>p</i>
Model 1			
Age (years)	1.0	.98 – 1.01	.87
Male gender	1.4	1.0 – 2.1	.05
Race (Black or other minority)	1.2	.85 – 1.8	.26
NYHA III/IV	1.7	1.2 – 2.3	.001
LVEF (%)	1.0	.98 – 1.01	.35
Comorbidity score	1.03	.94 – 1.1	.59
Prescribed anti-dyslipidemia	1.2	.8 – 1.6	.45
Non-obese/high inflammation	1.71	1.1 – 2.79	.03
Obese/low inflammation	1.2	.75 – 2.0	.44
Obese/high inflammation	1.71	1.1 – 2.7	.02
Model 2			
Age (years)	.99	.97 – 1.01	.21
Male gender	1.2	.78 – 1.8	.45
Race (Black or other minority)	1.13	.73 – 1.8	.58
NYHA III/IV	1.3	.89 – 1.9	.18
LVEF (%)	1.0	.99 – 1.02	.73
Comorbidity score	1.02	.92 – 1.1	.73
Prescribed Anti-dyslipidemia	1.09	.73 – 1.7	.67
NT-proBNP	2.2	1.5 – 2.7	< .0001
Non-obese/high inflammation	1.5	.86 – 2.7	.15
Obese/low inflammation	1.3	.72 – 2.3	.41
Obese/high inflammation	1.71	1.01 – 2.9	.046

NYHA; New York Heart Association, functional class LVEF; left ventricular ejection fraction, NT-proBNP; N-terminal pro-B-type natriuretic peptide.

Reference group: female gender, Caucasian ethnicity, NYHA functional class I or II, non-prescribed aspirin, NT-proBNP < 551 fmol/ml, non-obese with low inflammatory status