2010

SURVIVAL AND INFLAMMATION IN PATIENTS WITH HEART FAILURE: THE IMPACT OF OVERWEIGHT, OBESITY, DIABETES AND FRUIT AND VEGETABLE CONSUMPTION

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ABSTRACT OF DISSERTATION

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SURVIVAL AND INFLAMMATION IN PATIENTS WITH HEART FAILURE: THE IMPACT OF OVERWEIGHT, OBESITY, DIABETES AND FRUIT AND VEGETABLE CONSUMPTION

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Medicine at the University of Kentucky

By
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Lexington, Kentucky

Director: Dr. Terry A. Lennie, Associate Professor of Nursing

Lexington, Kentucky

2010

ABSTRACT OF DISSERTATION

SURVIVAL AND INFLAMMATION IN PATIENTS WITH HEART FAILURE: THE IMPACT OF OVERWEIGHT, OBESITY, DIABETES AND FRUIT AND VEGETABLE CONSUMPTION

Overweight and obesity are paradoxically associated with better survival in patients with heart failure (HF). This association is poorly understood, in part because the impact of diabetes (DM) on survival of overweight and obese HF patients has not been considered. Inflammation may contribute to worse survival in overweight and obese HF patients with DM, and levels of inflammation may be associated with fruit and vegetable consumption. However, neither of these relationships has been investigated in patients with HF.

The purposes of this dissertation were to a) examine the effect of DM on survival of overweight and obese patients with HF, b) explore potential inflammatory-related factors that underlie differences in survival of overweight and obese HF patients with and without DM and c) examine the association between nutrition and inflammation in patients with HF. To address these purposes three investigations were conducted: 1) comparison of event-survival (the combined endpoint of all cause hospitalization and death) of normal weight HF patients without DM to overweight and obese HF patients with and without DM 2) comparison of levels of inflammatory markers in overweight and obese patients with DM to normal weight, overweight and obese patients without DM 3) determination of the association of fruit and vegetable consumption with levels of inflammatory markers in patients with HF.

In the presence of DM, patients who were overweight and obese had increased risk of all cause hospitalization and death. Obese patients without DM had similar risk as normal weight patients without DM. Overweight and obese patients with DM had higher levels of some, but not all, inflammatory markers compared with normal weight, overweight and obese patients without DM. Higher vegetable, but not fruit consumption was associated with lower levels of some inflammatory markers.

This dissertation has addressed an important gap in the current evidence by demonstrating the contribution of DM to all cause hospitalization and death in overweight and obese patients with HF. This investigation has also demonstrated that higher levels of inflammation may contribute to differences in survival between these groups.

Increasing vegetable consumption may be one avenue to lowering inflammation in patients with HF.

KEYWORDS: heart failure, obesity, diabetes, inflammation, nutrition

Heather Payne-Emerson
Student's Signature

July 9, 2010
Date

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July 9, 2010

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DISSERTATION

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For Scott

ACKNOWLEDGMENTS

I would like to thank the members of my committee Dr. Terry Lennie, Dr. Debra Moser, Dr. Maria Boosalis and Dr. Geza Bruckner, for their guidance in developing and completing this project. I would especially like to thank my committee chair and mentor, Dr. Terry Lennie. Thank you for providing moral support, critiquing my papers and always being generous with your time, resources and advice. You have pushed me to be a better student and researcher, and I am deeply grateful for this. I would also like to thank Dr. Debra Moser who has provided me with many resources and opportunities over the last four years. It has been an honor to be a part of her team. Dr. Geza Bruckner, committee member and Director of Graduate Studies, has provided essential help in navigating the process of completing my PhD. Thanks also to Dr. Maria Boosalis for providing wonderful, practical nutrition expertise. I would also like to thank Dr. David Randall for serving as outside examiner.

There are also several organizations that have provided financial support for this project. The National Institutes of Health T32 Training Grant in Nutrition and Oxidative Stress has provided my fellowship and financial support. The University of Kentucky P20 Center for Biobehavioral Research on Self-Management in Cardiopulmonary Disease provided support for the intellectual contributions of several of the co-authors of the manuscripts within this dissertation. The National Institutes of Health, National Institutes for Nursing Research R01 NR 009280 and the University of Kentucky General Clinical Research Center M01 RR02602 provided funding for the investigations presented in Chapters Two, Three and Four.

I would like to acknowledge Dr. Susan Pressler and Dr. Sandra Dunbar for their oversight of data collection at Emory University and Indiana University. I would also like to acknowledge the RICH Heart research team. This project would not have been

possible without their work recruiting, assessing and following patients. Their labor and dedication are deeply appreciated.

There are several people in my life who have provided much love and support while completing my PhD. First, I thank my parents for pushing me to do my best at every endeavor, and thanks to my mom for the millions of prayers she has prayed to keep me safe and well. My brothers, sisters, brothers-in-law, sisters-in-law, nieces, nephews, parents-in-law and friends have filled my life with love, laughter, kinship and a sense of meaning. I would not have been able to complete this PhD without these gifts. Thanks especially to my sister Holly for critiquing cover letters, my CV and for giving me the inside scoop on interviewing for faculty positions. Most importantly, she has provided excellent advice and always made time to listen.

Above all others I would like to thank my husband, Scott. Thank you for being my steady, constant partner during these tumultuous four years. Thank you for bringing such joy to my life. Thank you for loving me so well.

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CHAPTER ONE:

Introduction

1. The impact of overweight, obesity and diabetes on survival of patients with heart failure

Heart failure (HF) affects 5.8 million people in the United States (U.S.), and 670,000 new cases are diagnosed each year.[1] The estimated direct and indirect cost of HF for 2010 is $39.2 billion,[1] but more importantly HF is also costly in terms of morbidity and mortality. It is the fourth most common cause of hospitalization in the U.S.,[2] and approximately 59% of men and 45% of women die within five years of HF diagnosis.[1]

Investigators in the Framingham Heart Study identified overweight and obesity as risk factors for the development of HF. After adjusting for known risk factors, investigators found that obesity doubled the risk for the development of HF among the 5581 participants. In women, overweight increased risk by 50%.[3] In contrast with our current understanding of the effects of overweight and obesity on morbidity and mortality,[4] the results of nine studies involving over 130,000 patients with HF demonstrated that overweight and obese patients have better survival compared with normal weight patients.[5-13]

Several putative explanations exist for this paradoxical relationship. Obesity may provide an increased metabolic reserve that helps patients withstand the catabolic stresses of HF. Obese patients may have lesser increases in neurohormonal activation, increased tolerance to angiotensin converting enzyme inhibitors, altered inflammatory cytokine profiles or higher cholesterol levels that may decrease inflammation. All of these may confer a better prognosis to overweight or obese patients with HF,[11, 14] but none have been tested which limits our understanding of the mechanisms underlying the obesity paradox.

Another factor limiting understanding of the obesity paradox is that the impact of obesity associated comorbidities, such as diabetes (DM) on survival of overweight and obese patients has not been considered. DM is a common comorbidity in patients with HF, with prevalence rates as high as 30%,[15] and it is associated with increased risk of death[16-23] and HF hospitalization[16, 17, 19] in patients with HF. The majority of the previous investigators of the obesity paradox have controlled for DM in survival analysis.[5, 7, 10-12] Consequently, the results of these studies reflect survival of overweight and obese patients independently of DM. No investigation has yet examined outcomes in

overweight and obese patients with DM compared to normal weight patients without DM, and as such the impact of DM among these groups is unknown.

The current evidence on the obesity paradox is further limited because most investigators have examined only all cause or cardiac related death.[5-9] Two groups have investigated all cause hospitalization[10, 12] and only one has examined the combined endpoint of all cause hospitalization and death.[11] All three controlled for the presence of DM; as a result the impact of DM on this outcome has been obscured. Because overweight, obesity[24-26] and DM[27, 28] can contribute to cardiac and non-cardiac morbidity[24, 27] and mortality,[25-28] it is important to look at both hospitalization and death from cardiac and non-cardiac causes in overweight and obese patients with and without DM. Studies of this type would provide a more complete picture of survival.

These gaps in the available evidence have contributed to a lack of consensus regarding body weight recommendations among the HF management guidelines. The American Heart Association/American College of Cardiology guidelines are silent regarding body weight recommendations for overweight and obese patients.[29] The European Society of Cardiology guidelines suggest weight loss for obese patients only,[30] while the Heart Failure Society of America recommends weight loss only for those with obesity associated syndromes such as obesity cardiomyopathy or obesity hypoventilation syndromes.[31] Studies examining the impact of DM on all cause hospitalization and death of overweight and obese patients with HF are needed to address current knowledge gaps and inform sound body weight recommendations in patients with HF.

2. Inflammation in heart failure and diabetes

Higher levels of inflammation in overweight and obese HF patients with DM may contribute to poorer survival, either through effects on the myocardium or through contribution to DM related microvascular complications. Levine et al[32] published one of the first studies demonstrating elevated levels of tumor necrosis factor alpha (TNFα) in patients with HF. In 33 patients with chronic HF, mean TNFα levels were 13 times higher than levels in age-matched healthy controls. Subsequently, several other investigators have found higher levels of TNFα[33-36] and its two soluble receptors, sTNF-R1[37-40] and sTNF-R2,[33, 35, 38, 39] in patients with HF. TNFα may contribute to the progression of HF through its negative inotropic effects and by contributing to cardiac remodeling.[41] Higher levels of TNFα[42] and its soluble receptors[40, 43] are predictive of worse survival in patients with HF.

Higher levels of TNFα have also been reported in patients with DM compared with non-DM controls.[44-47] Although its role is still being clarified, TNFα may contribute to the complications associated with DM including retinopathy,[48] neuropathy[49] and nephropathy.[50] Higher levels of TNFα,[51-53] sTNF-R1 and sTNF-R2[54] have been demonstrated in DM patients with these complications compared with DM patients without these complications. Further, mouse models suggest that increased levels of reactive oxygen species (ROS) may be present in the DM heart.[55] Oxidative stress not only promotes myocardial injury directly, but can also induce increases in inflammation.[56]

Higher levels of inflammation in overweight and obese HF patients with DM may be an underlying reason for differences in survival among these groups. However, investigators exploring inflammatory markers in patients with HF have not investigated the impact of DM on levels of inflammation. Similarly, none of the investigations exploring inflammatory markers in DM patients have been conducted in patients with HF as a comorbidity. Research is needed to determine if overweight and obese HF patients with DM have higher levels of inflammation compared with HF patients without DM. Exploring this question will help to identify potential avenues for improving outcomes in HF patients with DM.

3. Fruit and vegetable consumption and inflammation

Fruits and vegetables may provide an avenue for altering the inflammatory status of HF patients with and without DM, potentially through their antioxidant compounds. Oxidative stress promotes the binding of the transcription factor nuclear factor-kappa B (NF-κB) to DNA and the subsequent production of proinflammatory cytokines.[57] Antioxidants inhibit oxidative stress by neutralizing free radicals and reactive oxygen species[58] and may thereby block the synthesis of inflammatory cytokines and subsequent inflammation. Several nutrients found in fruits and vegetables have antioxidant capabilities such as vitamin C, vitamin E and the carotenoids (i. e. beta-carotene, lycopene, zeaxanthin, lutein).[58] However, fruits and vegetables are also sources of other phytochemicals including polyphenols,[59] which demonstrate antioxidant and anti-inflammatory properties such as inhibiting NF-κB.[60] Thus fruits and vegetables contain a variety of compounds that may alter inflammatory status.

Several studies have demonstrated that higher fruit and vegetable consumption is associated with lower levels of inflammatory markers in non-HF populations. Gao and collegues[61] investigated this relationship in 599 elders. A significant dose-response between increasing fruit and vegetable intake and decreasing plasma C-reactive protein

levels was demonstrated after controlling for the presence of DM and cardiovascular disease. Subsequent studies have also demonstrated this relationship for fruits[62, 63] and vegetables.[63] More recently the association between fruits and vegetables and TNFα has been investigated. Holt et al[64] demonstrated that TNFα levels were inversely associated with vegetable consumption in 285 adolescents after controlling for age, gender, race, energy intake and body mass index. This relationship has not been investigated in patients with HF, but has important implications for this patient population. TNFα is a primary contributor to the pathogenesis of HF[65] and higher levels of TNFα have been associated with poorer survival of patients with HF.[40, 42, 43] Investigating the association between fruit and vegetable consumption and levels of TNFα could identify a means of lowering inflammation and improving survival in patients with HF.

In sum, overweight and obesity are associated with better survival in patients with HF, but our understanding of this relationship is limited, in part because the impact of DM on all cause hospitalization and death of overweight and obese patients has not been investigated. Higher levels of inflammatory cytokines may contribute to worse survival in overweight and obese HF patients with DM either through effects on the myocardium or by contributing to microvascular damage. Although higher levels of inflammatory markers have been documented both in patients with HF and in patients with DM compared to normal controls, no study has yet investigated whether HF patients with DM have higher levels of inflammatory markers compared to HF patients without DM. In addition, levels of inflammatory markers have been associated with fruit and vegetable consumption, however it is unknown if this association exists in patients with HF. Identifying this relationship could provide a potential route to lowering inflammation and improving survival in HF patients with and without DM.

Therefore the purposes of this dissertation were to 1) examine the effect of DM on survival of overweight and obese patients with HF 2) determine differences in inflammation of overweight and obese HF patients with and without DM and 3) determine if fruit and vegetable consumption was associated with levels of inflammation in patients with HF. Three studies were conducted to address these purposes. First, the impact of DM on all cause hospitalization and death of overweight and obese patients was determined by comparing survival of normal weight HF patients without DM to overweight and obese HF patients with and without DM. Second, levels of inflammatory markers in overweight and obese patients with DM were compared to levels in normal

weight, overweight and obese patients without DM. Third, the association of fruit and vegetable consumption with levels of inflammatory markers in all patients with HF was determined.

4. Summary of chapters

Chapter Two is an investigation of the impact of DM on survival of overweight and obese HF patients. Three hundred thirty-eight patients recruited from HF clinics were stratified into five groups (normal weight without DM, overweight without DM, overweight with DM, obese without DM and obese with DM) and followed for a maximum of four years (mean follow-up time of 389 days). Hospitalization and death were determined by patient/family interview and medical record review. Cox regression analysis was used to determine differences in the combined endpoint of all cause hospitalization and death. Survival of overweight and obese patients with and without DM was compared to normal weight patients without DM. The results demonstrated that overweight and obese HF patients with DM and overweight patients without DM had double the risk of having an event compared with normal weight patients. However, obese patients without DM had similar survival compared with normal weight patients.

Chapter Three is a comparison of levels of inflammatory markers in overweight and obese patients with and without DM to normal weight patients without DM. A total of 343 patients were recruited from HF clinics and were again stratified into five groups (normal weight without DM, overweight without DM, overweight with DM, obese without DM and obese with DM). Plasma levels of sTNF-R1 and sTNF-R2 were determined in all patients. Obese patients with DM had significantly higher levels of sTNF-R1 compared with all three non-DM groups. Similarly, overweight patients with DM had significantly higher levels of sTNF-R1 compared with overweight and obese patients without DM. Obese patients with DM had significantly higher levels of sTNF-R2 compared with overweight and obese patients without DM, but there were no differences in sTNF-R2 levels between overweight DM patients and any group.

Chapter Four is an investigation of the association between fruit and vegetable consumption and levels of sTNF-R1 and sTNF-R2 in patients with HF. A total of 221 patients with HF were recruited from HF clinics. Fruit and vegetable consumption was determined using weighed four day food diaries, and plasma levels of sTNF-R1 and sTNF-R2 were measured in all patients. Logistic regression controlling for age, gender, NYHA class, DM, body mass index, waist circumference and energy intake revealed that higher vegetable, but not fruit consumption was associated with a lower risk of having

elevated sTNF-R1 levels. Fruit and vegetable consumption was not associated with higher levels of sTNF-R2.

Chapter Five is a synthesis of the results of the preceding chapters and a discussion of how this body of work advances the state of the science regarding obesity, DM, inflammation and nutrition in patients with HF. Clinical and research implications are also discussed.

CHAPTER TWO:

Increased Risk of All Cause Hospitalization and Death in Overweight and Obese Patients with Heart Failure: The Impact of Diabetes as a Comorbidity

1. Synopsis

Overweight and obesity are paradoxically associated with better survival in patients with heart failure (HF). However, overweight and obesity are also associated with diabetes mellitus (DM), a comorbidity that increases risk of hospitalization and death in patients with HF. The impact of DM on survival of overweight and obese HF patients with DM has not been described.

The purpose of this investigation was to compare event-free survival (all cause hospitalization and death) of overweight and obese HF patients with and without DM to normal weight patients without DM.

A total of 338 patients recruited from HF clinics were followed for hospitalization and death. Weight and height were measured using professional grade scales and stadiometers. Body mass index (BMI) was calculated as weight in kilograms/height in meters^2. The diagnosis of DM was determined by patient report and confirmed by medical record review. Patients were stratified into 5 groups: normal weight (18.5-24.9 kg/m^2) without DM (n=54), overweight (25-29.9 kg/m^2) without DM (n=60), overweight with DM (n=36), obese (≥ 30 kg/m^2) without DM (n=92) and obese with DM (n=96). Cox regression was used to compare differences in event-free survival among groups.

Forty-one percent of patients experienced an event. There was no significant difference in all cause hospitalization and death between obese patients without DM and normal weight patients without DM controlling for age, gender, NYHA class, LVEF, ACE inhibitor use, and depressive symptoms (p=.2). In contrast, obese patients with DM, overweight patients with DM and overweight patients without DM had double the risk for all cause hospitalization and death compared to the normal weight group (HR=2.09 95% CI=1.14-3.83; HR= 2.05 95% CI =1.02-4.12; HR=2.13, 95% CI=1.12-4.05).

The results of this investigation suggest that obesity does not increase risk of all cause hospitalization and death in patients with HF. However, obese patients with DM and overweight patients with and without DM are at increased risk for all cause hospitalization and death.

2. Introduction

Results of the Framingham Heart Study demonstrated that greater body mass index is independently associated with increased risk of heart failure (HF).[1] These

results are in line with our current understanding of the contribution of overweight and obesity to mortality and morbidity.[2, 3] In contrast, recent evidence indicates that overweight and obese patients with established HF have *decreased* mortality risk when compared with normal weight patients with HF.[4-12] This counterintuitive relationship has been described as the obesity paradox.

Overweight and obesity are also associated with increased risk for diabetes mellitus (DM).[2] DM is a common comorbidity in patients with HF with prevalence rates estimated as high as 30%.[13-16] DM increases the risk for hospitalization[17-19] and all cause mortality[14, 17-24] in patients with HF. The majority of investigators demonstrating the obesity paradox controlled for the presence of DM in their analyses.[4, 5, 8, 10, 11] Subsequently the contribution of DM to outcomes has not been examined. Similarly, the majority of investigators examining the impact of DM on outcomes in patients with HF have controlled for body mass index (BMI),[17, 19-21, 23, 24] but none considered the contribution of overweight and obesity to outcomes among patients with and without DM. To increase our understanding of the relationship between obesity and outcomes in HF investigators need to examine, rather than control for, the contribution of comorbidities to outcomes of overweight and obese patients with HF.

Furthermore, the majority of the previous investigations of the obesity paradox have examined all cause death or cardiac related death.[5-9, 12] Those that have examined all cause hospitalization have controlled for DM in their survival analyses.[4, 10, 11] However, overweight, obesity[3, 25] and DM[26, 27] can contribute to both cardiovascular[3, 26, 28] and noncardiovascular[3, 29] morbidity[3] and mortality.[25, 26] Thus, examining the combined endpoint of all cause hospitalization and death is necessary to completely characterize survival in overweight and obese HF patients with and without DM.

The purpose of this prospective study was to compare event-free survival (combined endpoint of all cause hospitalization and death) of overweight and obese HF patients with and without DM to normal weight HF patients without DM. Patients were divided into five groups according to BMI and the presence or absence of DM: normal weight without DM, overweight without DM, overweight with DM, obese without DM and obese with DM. Patients were followed for a mean of 389 days to determine differences in event-free survival among groups.

3. Methods

3.1 Sample

A total of 338 patients with HF were recruited from cardiology clinics at five academic medical centers in Kentucky, Indiana, Georgia, Ohio, and Australia. To participate, patients had to meet the following eligibility criteria: a) documented diagnosis of chronic HF with either preserved or non-preserved systolic function, b) stable on medications for three months, c) able to read and speak English, and d) no obvious cognitive impairment. Patients were excluded from the study due to a) HF etiology of rheumatic heart disease or pregnancy, b) comorbid terminal illness, c) stroke or myocardial infarction within the prior three months, or d) body mass index classified as underweight (BMI < 18.5 kg/m^2). Only seventeen normal weight patients recruited into the study had DM, comprising four percent of the sample. Thus this group was not included in data analysis due to insufficient sample size.

3.2 Measurement of variables

3.2.1 Body mass index and diabetes

Weight and height were measured in light clothing without shoes using professional grade scales and stadiometers. BMI was calculated as weight in kilograms divided by height in meters squared. BMI categories were determined using the National Heart Lung and Blood Institute guidelines (normal weight 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obese ≥ 30 kg/m^2).[30] The presence of DM was determined by self-report and medical chart review.

3.2.2 Event-free survival

The primary outcome of the study was event-free survival, defined as the combined endpoint of all cause hospitalization and death**.** Research assistants interviewed patients monthly by phone to ascertain hospitalizations. To increase accuracy of data, patients were asked to keep a diary with dates of all hospital admissions, and these data were verified by yearly medical record review performed by a research nurse. Dates and causes of death were determined by a combination of medical record review, family interview, and county death records. Patients were followed for a maximum of four years, with a mean follow-up time of 389 days.

3.2.3 Depressive symptoms

The presence of depressive symptoms may contribute to readmission for HF and increased mortality in patients with HF.[31, 32] Thus we chose to measure depressive symptoms and control for them in survival analysis. To assess depressive symptoms

research nurses administered the Beck Depression Inventory-II (BDI), a validated and reliable tool[33] that has been used to predict mortality in patients with HF.[32] The BDI is a 21 item self-report instrument that is designed to measure the severity of depressive symptoms. Patients rate their symptoms on a scale of 0 (absence of symptom) to 3 (persistent or severe symptom). Questions are summed to derive a total score (0-63) with higher scores indicating higher depressive symptoms.[34]

3.2.4 Other variables of interest

Research nurses determined age, gender, and New York Heart Association (NYHA) functional class through patient interview. Medications were also determined by patient interview and verified using the medical record. Most recent ejection fraction was obtained by medical record review.

3.3 Procedure

Approval of the study was obtained from the Institutional Review Board at each study site. Patients were screened for eligibility by research nurses and approached during clinic visits. Research nurses then obtained informed written consent and scheduled each patient an appointment at the General Clinical Research Center (GCRC) at the recruitment site. At the GCRC height and weight were measured by GCRC research staff, and research nurses interviewed patients regarding age, gender, NYHA class, medication use, depressive symptoms and DM. The medical record was reviewed to obtain the most recent ejection fraction and to verify medications and the presence of DM. Patients were followed by research assistants and a research nurse for hospitalizations and death as previously described.

3.4 Data analysis

Patients were categorized into five groups based on BMI category and the presence or absence of DM. Group comparisons of gender, NYHA class, and prescribed diuretics, beta blocker and angiotensin converting enzyme (ACE) inhibitors were determined using chi square statistic and standardized residuals. Comparisons of age, left ventricular ejection fraction (LVEF) and BDI score were determined using one-way analysis of variance (ANOVA) with Tukey's post hoc test.

Cox regression analysis was conducted to determine differences in event-free survival among the groups using normal weight patients without DM as the reference group. Variables entered into the model based on clinical relevance were age, gender, LVEF, NYHA class (I/II, III, IV), BDI score and ACE inhibitor use. All analyses were done

using Predictive Analytics Software version 16.0 and p values < .05 were considered statistically significant.

4. Results

4.1 Patient characteristics

Patient characteristics are displayed in Table 2.1. Obese patients without DM were younger than normal weight patients, overweight patients and obese patients with DM, while obese patients with DM were only younger than normal weight patients. Obese patients (with and without DM) had a higher EF than the normal weight patients. A greater percentage of patients taking diuretics were overweight with DM, obese without DM or obese with DM. There were no other statistically significant differences in patient characteristics among groups.

4.2 Event-free survival

A total of 138 (41%) patients experienced an event over a mean follow up time of 389 days. Of these 73 were cardiac related and 65 were non-cardiac related death or hospitalization (Table 2.2). The Cox regression model is displayed in Table 2.3. Survival curves are displayed in Figure 2.1.

Age and BDI score were significant predictors of event-free survival. For every one point increase in BDI score the risk of all cause hospitalization and death increased by four percent. There were also significant differences in survival among the DM and BMI groups. Overweight patients without DM, overweight patients with DM and obese patients with DM had double the risk for all cause hospitalization and death compared with normal weight patients without DM. In contrast, there was no difference in survival of obese patients without DM compared with normal weight patients without DM.

5. Discussion

This was the first study to examine the impact of overweight and obesity in combination with DM on survival outcomes of patients with HF. We demonstrated that in the presence of DM overweight and obese patients were at increased risk for all cause hospitalization and death. Furthermore, the event-free survival that we observed in the obese and overweight groups without DM differed from those observed in prior investigations. The investigators in these studies demonstrated that overweight and obese patients with HF had better survival than normal weight patients while controlling for the presence of DM.[4, 6, 8, 10, 11] We demonstrated that obese patients without DM had similar, rather than better, survival compared with normal weight patients without DM.

Additionally, overweight patients without DM had worse survival compared with the normal weight group.

Perhaps the most important difference between our study and each of these previous investigations on the obesity paradox was the chosen follow-up endpoint. Horwich et al[5] evaluated only cardiac related mortality in systolic HF patients referred for heart transplant evaluation and found that overweight and obese patients had better survival at 2 years and similar survival at 5 years. Lavie et al,[6] Gustafsson et al,[8] Davos et al[9] and Arena et al[12] used all cause mortality or cardiac related mortality as the outcome in survival analyses of patients with less advanced HF, and all demonstrated lower risk in overweight and obese patients. Two of the three remaining investigations on the obesity paradox, those conducted by Curtis et al[4] and Bozkurt et al,[11] examined all cause hospitalization as one of the outcomes investigated in the study. These investigators found no difference in risk for all cause hospitalization among BMI groups, however DM was controlled for in all of these analyses thus obscuring the contribution of DM to this outcome.

In contrast we examined the combined endpoint of all cause hospitalization and death. Obesity[3] and DM[27, 29] contribute to morbidity[3, 27, 29] as well as mortality,[25, 26, 28] and thus examining only death or cardiac related death would have provided an incomplete picture of survival. Secondly, overweight, obesity[3, 28] and DM[26, 27, 29] contribute to both cardiovascular[26, 28] and noncardiovascular[3, 27, 29] morbidity and mortality, and thus examining only cardiac related events would have provided an incomplete picture of survival as well. In our study, 47% of events were due to reasons other than HF or other cardiovascular causes. If we had chosen to only examine cardiac related outcomes we would have neglected nearly half of the events that occurred. The use of the combined endpoint of all cause hospitalization and death is necessary to fully characterize survival in overweight and obese patients with HF and to aid health care professionals in making weight recommendations for these patients.

There has been only one study, by Kenchaiah et al[10] that investigated the combined endpoint of all cause hospitalization and death as in our study. This was an analysis of 7599 patients enrolled in the Candesartan in Heart Failure: Assessment of Reduction of Mortality and Morbidity (CHARM) program. Cox regression analysis showed no difference in all cause hospitalization and death among BMI groups after controlling for the presence of DM. Similarly, we found that obese patients without DM had similar risk compared with normal weight patients without DM. However, our results

contrast with these in that overweight patients without DM were at higher risk. The reasons for these differences in results are unclear. It may be speculated that not all events were captured in one or both of these studies. The CHARM trial did not specify their methods for determining events and as such we cannot speculate on the completeness of their survival data. However, we used multiple approaches to determine dates and causes of events: monthly patient interview to capture events that occurred outside of the primary hospital site and medical record review to verify the dates and causes of these events. For this reason, our data provide a more comprehensive assessment of event-free survival. It should be noted that the investigation by Kenchaiah et al[10] was initiated more than 10 years ago. With the exception of one study examining cardiac mortality,[12] all of the earlier investigations of the obesity paradox were initiated 14-19 years ago[4, 6, 8, 9, 11] and in one instance nearly 30 years ago.[5] The management of HF continues to advance[35] and data gathered for these analyses may not represent outcomes of HF patients treated with current therapies.

There has been some suggestion that the relationship of BMI to outcomes may vary by the presence of preserved and nonpreserved systolic function. Gustafsson et al[8] found that in patients with systolic HF, the overweight and obese groups had worse survival compared with normal weight groups, while in those with preserved systolic function obese patients had improved outcomes. Our study included both patients with preserved and nonpreserved EF. However, multiple other investigations have found improved survival with higher BMI in those with systolic HF[5, 6, 36] or after stratifying by EF.[4, 10, 11] Thus it is unlikely that our inclusion of patients with both preserved and nonpreserved EF contributed to these differences.

Our results also confirmed the observation that patients with HF and DM have shorter event-free survival than patients without DM. Both overweight patients with DM and obese patients with DM were at increased risk for all cause hospitalization and death. The Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry[18] produced some of the first data on survival of patients with both HF and DM. In this trial of 12,873 patients, DM was an independent predictor of all cause mortality, HF hospitalization and all cause hospitalization over one year follow up. Several other large retrospectively analyzed clinical trials have found similar results over longer follow up times.[14, 19] In addition to clinical trials, population studies[20, 21] have also shown that patients with both HF and DM have higher risk of all cause death. Although BMI was controlled for in the survival analyses of some of these clinical trials and population

studies,[17, 19-21, 23, 24] this is the first study to investigate the impact of DM on outcomes of overweight and obese HF patients in comparison with normal weight non-DM HF patients.

5.1 Limitations

Several limitations in our study are noted. First, the mean follow-up time for our study was 389 days or 13 months. Although we followed patients for a maximum of 4 years, our results may be more representative of short-term rather than long-term outcomes. Second, we did not use diagnostic measures such as oral glucose tolerance testing to determine the presence of DM. Rather, this information was gathered through self-report and verified using the medical record if patients were uncertain if they had this diagnosis. It is possible that some patients may have been unaware that they had DM or were not yet diagnosed and may have been incorrectly grouped as overweight non-DM or obese non-DM. As a result the overweight non-DM group may have included uncontrolled DM causing this group to have greater risk compared to the normal weight non-DM group. Similarly, the inclusion of uncontrolled DM patients in the obese non-DM group may have caused this group to appear to have similar, rather than better survival compared to the normal weight group without DM. We also did not collect data on blood glucose control such as hemoglobin A1c, and consequently we do not know how well controlled patients with DM were. Research investigating the impact of blood glucose levels on survival of overweight and obese HF patients with DM is needed.

6. Conclusions

In the presence of DM overweight and obese HF patients were at increased risk for all cause hospitalization and death compared with normal weight HF patients without DM. Overweight patients without DM were also at increased risk. In contrast, obesity in the absence of DM did not contribute to worse survival, suggesting that obesity in the absence of DM does not convey greater risk of all cause hospitalization and death.

There is little guidance and little consensus among current HF management guidelines regarding weight loss recommendations for overweight and obese patients. The American College of Cardiology/American Heart Association guidelines are completely silent regarding weight loss recommendations for both overweight and obese patients.[35] The European Society of Cardiology HF management guidelines recommend weight loss for obese patients only,[37] while the Heart Failure Society of America recommends weight loss only for patients with obesity related syndromes such as

obesity-cardiomyopathy or obesity-hypoventilation syndromes.[38] No recommendations are made for overweight patients in any of these guidelines.

This lack of consensus reflects the current level of evidence regarding survival of overweight and obese patients with HF. Our understanding of this relationship has been limited by two gaps in the available evidence: 1) the contribution of obesity associated comorbidities, such as DM, to survival of overweight and obese patients was not investigated and 2) previous investigators did not consider the impact of overweight and obesity on all cause hospitalization and death. Rather, previous investigators considered only death, cardiac related death or hospitalizations after controlling for DM. Our investigation addressed both of these gaps and clarified the paradoxical relationship between overweight and obesity and survival by examining the contribution of DM to all cause hospitalization and death. This new evidence will assist with development of more comprehensive body weight recommendations for patients with HF.

Table 2.1 Patient characteristics by body mass index and diabetes group

Patient characteristics	Normal weight non-DM	Overweight non-DM	Overweight DM	Obese non-DM	Obese DM	*P* Value
	n = 54	n = 60	n = 36	n = 92	n = 96	
Gender, Women	19 (35)	15 (25)	10 (28)	36 (39)	31 (32)	.421
Age, years	66 ±12	62 ±11	67 ±11	56 ±12	61 ±9	≤ .001 [a,b,c,d,f]
LVEF, %	30 ±14	33 ±13	30 ±13	37 ±15	38±15	≤.002 [a,b,e]
NYHA Class						
--I/II	31 (57)	34 (57)	12 (33)	47 (51)	39 (41)	.093
--III	17 (32)	21 (35)	18 (50)	39 (42)	40 (42)	
--IV	6 (11)	5 (8)	6 (17)	6 (7)	17 (18)	
BDI	9.6 ± 7.8	10.7 ± 8.7	10.3 ± 9.8	10.1 (8)	12.2 (9.8)	.384
Diuretics	31 (59)	42 (70)	31 (86)	75 (82)	75 (76)	.008
Beta blocker	51 (94)	52 (87)	30 (83)	86 (94)	80 (83)	.101
ACE inhibitor	36 (67)	44 (73)	26 (72)	68 (74)	71 (74)	.888

Values are n (%) or mean ± standard deviation. a, normal weight versus obese non-DM; b, normal weight versus obese DM; c, overweight non-DM versus obese non-DM; d, overweight DM versus obese non-DM; e, overweight DM versus obese DM; f, obese non-DM versus obese DM.
DM, diabetic; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; BDI, Beck Depression Inventory; ACE, angiotensin converting enzyme.

Table 2.2 Number of cardiac and non-cardiac hospitalizations and deaths per group

Event	Normal weight non-DM	Overweight non-DM	Overweight DM	Obese non-DM	Obese DM	Total Sample
Cardiac	8(53)	19(68)	10(56)	20(65)	16(35)	73(53)
Non-cardiac	7(47)	9(32)	8(44)	11(35)	30(65)	65(47)
Total	15	28	18	31	46	138

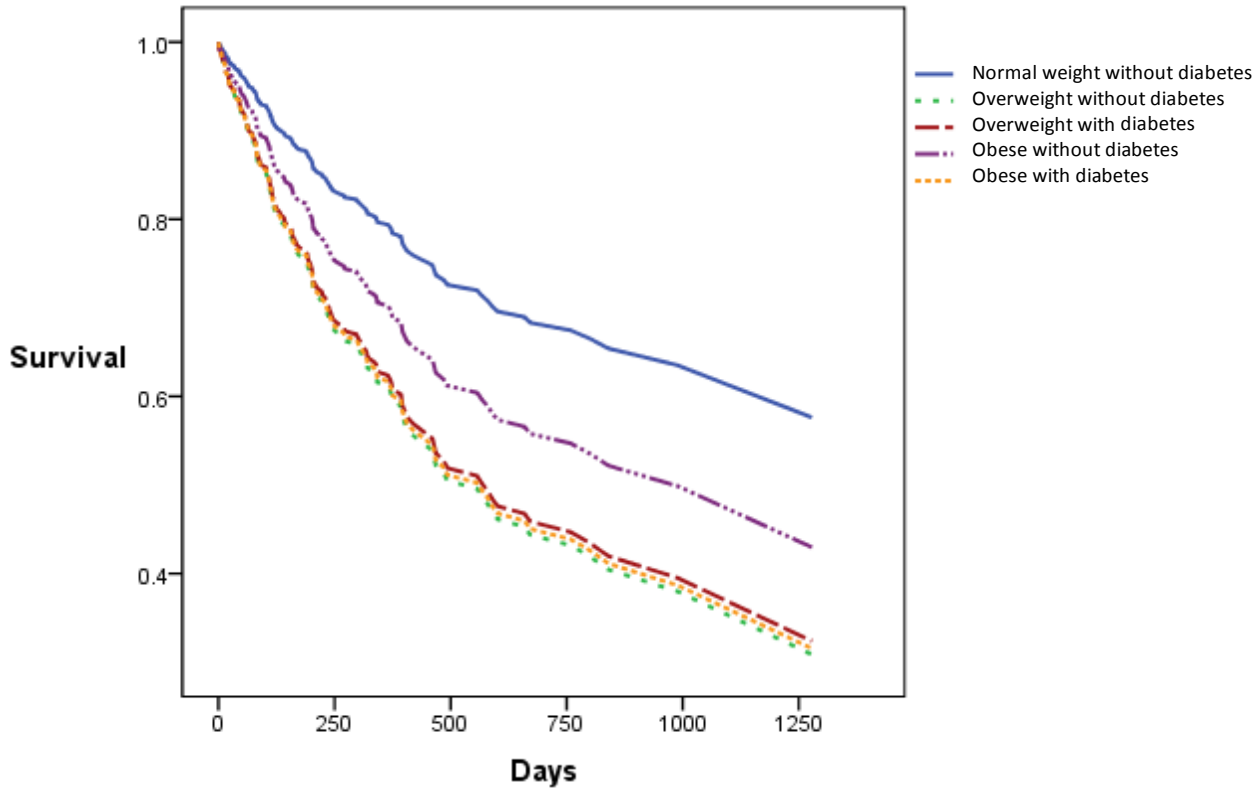
Values are n(%); DM, diabetic; cardiac, hospitalizations and deaths due to HF or other cardiovascular causes; non-cardiac, hospitalizations and deaths due to non-cardiovascular causes

Table 2.3 Hazard ratios for all cause hospitalization and death

Variable	Exp(B)	95% Confidence Interval		P Value
Age	1.01	1.0	1.03	.045
Gender	.93	.63	1.37	.701
NYHA IV	1.20	.72	2.00	.477
LVEF	.99	.98	1.00	.075
ACE inhibitor	.81	.55	1.19	.279
BDI	1.04	1.02	1.06	<.001
Overweight non-DM	2.13	1.12	4.05	.021
Overweight DM	2.05	1.02	4.12	.044
Obese non-DM	1.53	.80	2.93	.196
Obese DM	2.09	1.14	3.83	.017

NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; BDI, Beck Depression Inventory; DM, diabetic

Figure 2.1 Cox regression survival curve for body mass index and diabetes groups



CHAPTER THREE:

Higher Levels of Soluble TNF-alpha Receptors in Overweight and Obese Heart Failure Patients with Diabetes

1. Synopsis

Higher levels of inflammation may contribute to poorer event-free survival in overweight and obese HF patients with DM. TNFα and its soluble receptors may contribute to the development and progression of heart failure (HF). Similarly, TNFα contributes to the complications associated with diabetes (DM) and higher levels of inflammatory markers have been demonstrated in patients with DM compared with non-DM controls. Whether HF patients with DM have higher levels of inflammatory markers compared to HF patients without DM has not been investigated.

The purpose of this investigation was to compare levels of inflammatory markers (sTNF-R1 and sTNF-R2) among normal weight, overweight, and obese patients with HF with and without DM as a comorbidity.

A total of 343 patients were recruited from HF clinics. Fasting blood draws were taken and levels of sTNF-R1 and sTNF-R2 were measured by ELISA. Weight and height were measured using professional grade scales and stadiometers, and from these values body mass index (BMI) was calculated. The presence of DM was determined by patient interview and verified using the medical record. Patients were stratified into five groups: normal weight (18.5-24.9 kg/m^2) without DM (n=52), overweight (25-29.9 kg/m^2) without DM (n=63), overweight with DM (n=36), obese (≥ 30 kg/m^2) without DM (n=100) and obese with DM (n=92). Analysis of variance with Tukey's post hoc test was used to determine differences in inflammatory markers among groups.

Obese patients with DM had higher levels of sTNF-R1 compared with all non-DM groups (normal weight $p < .05$; overweight $p \leq .001$; obese $p \leq .001$). Overweight patients with DM had higher levels of sTNF-R1 compared with overweight ($p = .008$) and obese ($p = .008$) patients without DM. Levels of sTNF-R2 were higher in obese patients with DM compared with obese ($p \leq .001$) and overweight patients ($p \leq .001$) without DM. Overweight patients with DM did not have higher levels of sTNF-R2 compared with any group.

The results of this investigation demonstrate that diabetes is associated with higher levels of inflammatory markers in overweight and obese patients with HF. Higher levels of inflammation may contribute to worse event-free survival in obese HF patients with DM.

2. Introduction

Increased levels of proinflammatory cytokines have been reported in patients with heart failure (HF)[1-7] with higher levels associated with worsening New York Heart Association functional class.[2, 4-6] The proinflammatory cytokine tumor necrosis factor-alpha (TNFα)[2, 4-9] and its two soluble receptors, TNF receptor 1 (sTNF-R1) and TNF receptor 2 (sTNF-R2),[4-6, 8] are among the inflammatory markers commonly elevated in patients with HF. TNFα may promote the progression and clinical manifestations of HF[10, 11] through its negative inotropic effects and through its contribution to cardiac remodeling.[11, 12] Both TNFα[13] and its receptors[14, 15] have been shown to predict mortality in patients with HF.

Similarly, systemic inflammation is present in patients with diabetes (DM), a common comorbidity in patients with HF.[16-19] Several investigators have demonstrated that higher levels of TNFα[20-23] are present in patients with DM versus non-diabetic individuals. Although the role of TNFα is still being clarified,[24] it may contribute to insulin resistance[25] and the complications associated with DM.[24, 26-31]

The purpose of this study was to compare levels of inflammatory markers (sTNF-R1 and sTNF-R2) among normal weight, overweight, and obese patients with HF with and without DM as a comorbidity. Results from our previous work suggest that obese and overweight HF patients with DM were at increased risk for all cause hospitalization and death compared with normal weight HF patients without DM.[32] Consequently, we hypothesized that overweight and obese patients with HF and DM would have higher levels of inflammatory markers compared with normal weight, overweight and obese HF patients without DM. Higher levels of inflammatory markers may explain, in part, the shorter event-free survival we observed in patients with HF and DM. Patients were grouped according to the presence or absence of DM and by body mass index (BMI) categories.

3. Methods

3.1 Sample

A total of 343 patients were recruited from cardiology clinics at three academic medical centers: the University of Kentucky, Indiana University and Emory University. To be eligible for the study patients had to a) have documented chronic heart failure with either preserved or nonpreserved systolic function b) be stable on medications for three months c) be able to read and speak English and d) have no obvious cognitive impairment. Patients were excluded from the study if they had a) heart failure of

rheumatic or valvular etiology, b) a terminal illness, c) an autoimmune disease, d) a myocardial infarction within the last three months, or e) end-stage renal disease

3.2 Measurement of variables

3.2.1 Inflammatory markers

The two soluble receptors for TNFα, sTNF-R1 and sTNF-R2, were measured in all patients. After TNFα binding sTNF-R1 and sTNF-R2 may be internalized, but are also shed from the surface of cells and released into circulation.[10] Consequently, sTNF-R1 and sTNF-R2 are considered markers of TNFα activity.[10] Plasma levels of the soluble receptors and TNFα were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Alpco Immunoassays) in the core laboratory of the University of Kentucky General Clinical Research Center (GCRC). All samples were run in duplicate with the average of the samples used. Sample assays were repeated if the coefficient of variation was greater than 10%.

3.2.2 Body mass index and diabetes

Weight and height were measured in light clothing and without shoes using professional grade scales and stadiometers. BMI was calculated as weight in kilograms divided by height in meters squared. BMI categories were determined using the National Heart Lung and Blood Institute guidelines (normal weight 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, obese ≥ 30 kg/m^2).[33] The presence of diabetes was determined by self-report and verified by chart review.

3.2.3 Other variables of interest

Age, gender and New York Heart Association (NYHA) functional class were determined through patient interview. Medication use was determined through patient interview and verified using the medical record. Most recent ejection fraction and HF etiology were obtained by medical record review. Comorbidities were determined using the Charlson Comorbidity Index.[34] At enrollment patients were interviewed regarding the presence of comorbidities. Each comorbidity is assigned a point value based on the seriousness of each condition. Points are summed to derive a total score, which can range from 0-34. Total scores were used to compare differences among groups excluding DM. This instrument has been demonstrated to be a valid and reliable instrument.[34, 35] It has been shown to predict mortality, hospital length of stay, number of hospitalizations and hospital charges.[34, 35]

3.3 Procedure

Approval for the study was obtained from the Institutional Review Board at each study site. Patients meeting inclusion criteria were identified by clinic staff and approached during clinic visits. The study was explained, and written, informed consent was obtained for those agreeing to participate. Research nurses then scheduled patient appointments at the GCRC at their respective institutions. All appointments were made in the morning. Fasting blood draws were taken and height and weight were measured by GCRC research staff at these appointments. Research nurses interviewed patients to determine age, gender, NYHA class, medication use and comorbidity score. The medical record was reviewed by research nurses to verify medication use, the presence of DM, HF etiology and the most recent ejection fraction. Plasma collected at Emory University and Indiana University was frozen and shipped on dry ice to the GCRC core laboratory at the University of Kentucky and stored at -80° Celsius until analyzed for sTNF-R1 and sTNF-R2.

3.4 Data analysis

Patients were divided into five groups based on BMI and the presence or absence of DM: normal weight without DM, overweight without DM, overweight with DM, obese without DM and obese with DM. Only 15 normal weight patients had DM, making up only four percent of the total sample. Thus normal weight patients with DM were not included in the analysis due to insufficient sample size.

Differences in mean plasma levels of soluble receptors were determined using one-way analysis of variance (ANOVA) with Tukey's post hoc test. Because values were not normally distributed they were mathematically transformed for the purposes of analysis. Non-transformed values are reported. Differences in group characteristics were determined using chi square statistic for categorical variables or ANOVA for continuous variables. Predictive Analytics Software version 16.0 was used for all analyses with p values $< .05$ considered statistically significant.

4. Results

4.1 Patient characteristics

Characteristics for each group are displayed in Table 3.1. Obese patients were younger, had a higher EF and a greater percentage were of a minority than normal weight and overweight groups. There was a lower percentage of women in the overweight groups. Ischemic etiology was more common in the overweight DM group and least common in obese non-DM and obese DM groups. Patients with DM were more

frequently on a cholesterol lowering agent and had a higher mean comorbidity score. A greater percentage of overweight patients with DM and obese patients with and without DM were in NYHA classes III and IV.

4.2 sTNF-R1 and sTNF-R2

Differences in inflammatory marker values are displayed in Figures 3.1 and 3.2. The obese group with DM had higher sTNF-R1 levels than all three groups without DM, while the overweight group with DM had higher sTNF-R1 levels than the overweight and obese groups without DM (Figure 3.1). sTNF-R2 levels were higher in obese patients with DM compared with overweight and obese patients without DM. There were no significant differences in the overweight DM group compared with the three non-DM groups (Figure 3.2). Overweight and obese patients without DM had similar levels of both sTNF-R1 and sTNF-R2 compared with normal weight patients.

5. Discussion

This was the first study to compare levels of inflammatory markers in overweight and obese HF patients with DM to normal weight, overweight and obese HF patients without DM. sTNF-R1 levels were higher in obese HF patients with DM compared to all non-DM groups. Overweight DM patients also had higher levels of sTNF-R1 compared with overweight and obese non-DM patients. Similarly, higher levels of sTNF-R2 were present in obese patients with DM compared with overweight and obese patients without DM. These results partially confirm our hypothesis that patients with DM have higher levels of inflammatory markers than patients without DM. Higher levels of inflammation may be contributing to worse all cause hospitalization and death in obese HF patients with DM.

Higher levels of inflammatory markers, including TNFα, have been demonstrated in patients with HF.[2-5] Levine et al[1] published one of the first studies demonstrating higher TNFα levels in these patients. In 33 patients with chronic HF, mean TNFα values were 13 times higher than levels in age-matched controls. Several other investigators have also reported this relationship, both for TNFα[2, 4, 36] and its soluble receptors,[4-6, 8] but unlike our study, these levels were not compared among HF patients with and without DM. Similarly, higher levels of TNFα have also been reported in patients with DM versus non-DM controls,[20, 21] but these studies were not conducted in patients with HF.

Higher levels of TNFα in HF patients with DM may contribute to worse all cause hospitalization and death either through effects on the myocardium or through contribution to the microvascular complications associated with DM. In addition to

contributing to the cardiac remodeling and decreased myocardial contractility observed in HF,[10, 11] TNFα is also involved in the microvascular complications associated with DM,[37] such as diabetic retinopathy,[31] nephropathy[29] and neuropathy.[30, 38] Higher levels of TNFα have been demonstrated in DM with these complications in comparison to DM without these complications.[39-42]

Although prior investigators have demonstrated elevated levels of TNFα in patients with HF, it should be noted that in previous studies, TNFα was not consistently elevated. Dutka et al[9] measured TNFα in 16 NYHA class IV patients at three month intervals for one year. In all patients TNFα could not be detected on at least one occasion. Munger et al[3] were unable to detect any difference in TNFα values between NYHA class II-IV HF patients and individuals without HF, while Lommi and colleagues[43] were only able to detect significant differences in hepatic venous measures of TNFα, but not in peripheral measures. The results of these studies may be due to the fact that TNFα primarily operates in autocrine and paracrine manners[44] or has a short half-life of about 30 minutes.[45]

For these reasons we measured levels of the soluble receptors for TNFα. In contrast to the autocrine and paracrine manners in which TNFα operates,[44] the soluble receptors are cleaved from the surface of the cell and released into circulation after being bound by TNFα.[10] As a result these receptors can be used as markers of TNFα activity.[10] The roles of sTNF-R1 and sTNF-R2 are still being clarified, but recent studies in mice have suggested that sTNF-R1 mediates hypertrophy and the other cardiac remodeling effects of TNFα, while sTNF-R2 acts to ameliorate these effects.[46, 47] Given this it is interesting that sTNF-R1 levels were elevated in obese patients with DM, and this same group was also at greater risk of all cause hospitalization and death as demonstrated in our previous study.[32] Thus these higher levels of inflammation may partially explain why obese patients with DM had worse survival compared with normal weight non-DM patients.

Whether higher levels of inflammation in overweight DM patients contributed to worse all cause hospitalization and death in our previous study remains unclear from this investigation. Although the overweight DM group did demonstrate higher levels of sTNF-R1 compared with overweight non-DM and obese non-DM patients, this group did not have higher levels in comparison with normal weight patients. This lack of a statistically significant difference may be due to the relatively small sample size for overweight DM patients. This was the smallest group with only 36 patients in comparison with 52, 63,

100 and 92 patients in the normal weight, overweight non-DM, obese non-DM and obese-DM groups respectively.

We did not demonstrate the same differences in sTNF-R2 levels. Rather, levels of sTNF-R2 in obese DM patients were not different compared with the normal weight non-DM group and overweight patients with DM did not have higher levels compared with any group. The reasons for this are unclear. Because the soluble receptors are cleaved and released after TNFα binding,[10] one would expect that higher levels of TNFα would be reflected by higher levels of both soluble receptors. Given the autocrine and paracrine manners in which TNFα operates[44] it is tempting to speculate that TNFα production in patients with DM is higher only in those cells with a higher expression of sTNF-R1 but is produced at similar levels in those cells that preferentially express sTNF-R2. sTNF-R1 is constitutively expressed in virtually all cell types with the exception of erythrocytes while sTNF-R2 is preferentially expressed in endothelial and hematopoietic cells.[48] However, TNFα is involved in vascular dysfunction associated with DM,[27, 49] and thus it would be expected that endothelial expression of TNFα would be up-regulated in patients with DM, translating to increased levels of sTNF-R2. The greater likelihood is that our sample size was insufficient to demonstrate significant differences in sTNF-R2 levels. Larger sample sizes may be needed to demonstrate differences in sTNF-R2 levels among these groups.

It should also be noted that a greater percentage of the overweight and obese patients with DM were taking cholesterol lowering agents. Statins are a subclass of cholesterol lowering agents that have been demonstrated to lower plasma markers of inflammation.[50] Although we did not have data regarding the use of statins in this investigation, it is possible that a greater degree of use of these agents by patients with HF and DM could have caused these patients to have lower levels of sTNF-R1 and sTNF-R2 than would have been demonstrated otherwise. Future research controlling for the use of statins will provide a better understanding of the co-morbid effects of DM on levels of inflammation in patients with HF.

Finally, overweight patients without DM were also at greater risk for all cause hospitalization and death compared with normal weight non-DM patients, but this group did not have higher levels of any inflammatory marker. This indicates that inflammation may not be the only contributing factor to worse survival in overweight HF patients without DM. More studies are needed to determine other underlying causes of worse all

cause hospitalization and death in this group such as acute illness or infections that were not induced by higher levels of inflammation.

5.1 Limitations

We assessed DM through patient interview and verified this using the medical record rather than through more diagnostic measures such as oral glucose tolerance testing. It is possible that some patients may have been unaware that they had DM. As a result patients with DM could have been misclassified as non-DM in our study, leading to higher levels of inflammatory markers in the non-DM groups. Second, we did not measure hemoglobin A1c and therefore cannot make any conclusions about the influence of blood glucose control on inflammation in these patients. More research investigating this and the effect of blood glucose-lowering lifestyle interventions on inflammation in patients with HF are needed. Finally, we had a rather small sample size for some groups. Because of these small sample sizes we may not have been able to detect all differences in levels of soluble receptors between groups.

6. Conclusions

In conclusion, DM as a comorbidity is associated with higher levels of inflammation in patients with HF and may be an underlying contributor to increased hospitalization and death observed in obese HF patients with DM. However, we also found that overweight patients without DM were at increased risk for hospitalization and death, but higher levels of inflammation were not present in this group. This indicates that while inflammation may be contributing to worse event free survival among obese HF patients with DM, it may not be the sole underlying factor in the worse survival demonstrated in overweight patients without DM. Further research is needed to determine other causes for worse survival in overweight patients without DM. Future studies using larger sample sizes are needed to confirm the differences in inflammatory marker levels that we observed. Additionally, research investigating if these levels of inflammation are related to blood glucose control is needed.

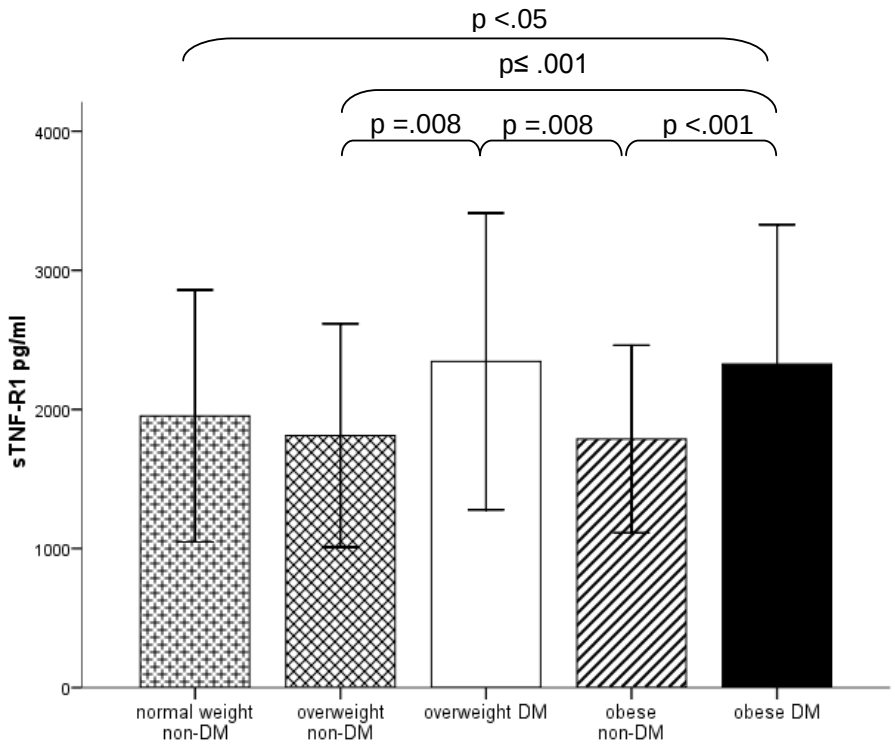
Table 3.1 Patient characteristics by body mass index and diabetes group

Patient characteristics	Normal weight non-DM n = 52	Overweight non-DM n= 63	Overweight DM n = 36	Obese non-DM n=100	Obese DM n=92	P value
Age, years	64 ± 11	63 ± 13	63 ± 13	56 ± 13	59 ± 10	≤.01[abcd]
Female	22 (42)	12(19)	6(17)	44(44)	31(34)	.002
NYHA class						.001
I/II	37 (73)	44(70)	17(47)	52(53)	40(44)	
III/IV	14 (28)	19(30)	19(53)	47(48)	52(57)	
N=341						
Ischemic etiology N=319	21(46)	27(46)	22(65)	32(35)	36(41)	.049
LVEF, % N=320	31 ± 14	35±15	31 ± 14	38 ± 15	37 ± 15	<.05[a]
ACE inhibitor N=334	29 (59)	43(69)	30 (83)	66(67)	66(75)	NS
ARB N=333	6 (12)	11(18)	4(11)	17(18)	21(24)	NS
Beta blocker N=339	48 (94)	53(84)	31(86)	90(90)	78(88)	NS
CLA N=340	34(65)	42(68)	32(89)	49(50)	75(82)	<.001
Minority	6(12)	9(14)	3(8)	37(37)	32(35)	<.001
Charlson comorbidity	2.1 ± 1.4	2.1 ± 1.5	2.4 ±1.3	1.9 ± 1.2	2.8 ± 1.6	<.001 [e]

Values are n(%) or mean ± standard deviation. a. normal weight vs. obese non-DM b. overweight non-DM vs. obese non-DM c. overweight DM vs obese non-DM d. overweight DM vs. obese DM e. obese DM vs. normal weight, overweight non-DM and obese non-DM

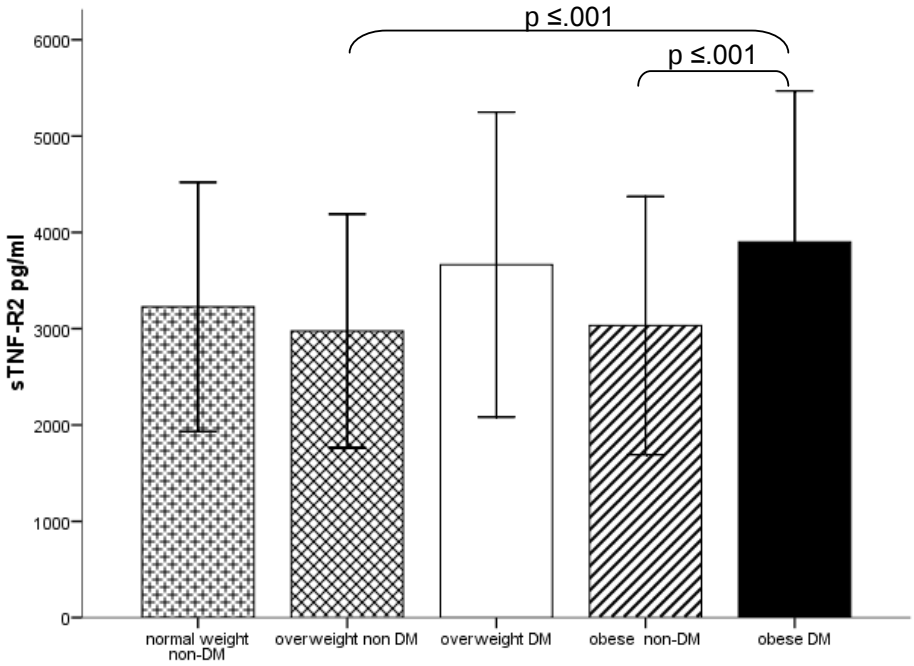
DM, Diabetic; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CLA, cholesterol lowering agent

Figure 3.1 Mean sTNF-R1 values for body mass index and diabetes groups



Significant differences between groups were determined using Tukey's post hoc test using log transformed variables.

Figure 3.2 Mean sTNF-R2 values for body mass index and diabetes groups



Significant differences between groups determined using Tukey's post hoc test using square root transformed variables.

CHAPTER FOUR:

Higher Vegetable Consumption is Associated with Lower Levels of Soluble TNF-alpha Receptor 1 in Patients with Heart Failure

1. Synopsis

TNFα and its soluble receptors may contribute to the progression of heart failure (HF). Higher consumption of fruits and vegetables has been associated with lower levels of TNFα and other markers of inflammation in the general population. However, this relationship has not been investigated in patients with HF.

The purpose of this investigation was to determine if higher fruit and vegetable consumption is associated with lower levels of inflammatory markers (sTNF-R1 and sTNF-R2) in patients with HF and to identify differences in other food groups among HF patients with lower and higher levels of inflammatory markers.

A total of 221 patients completed weighed four-day food diaries that were reviewed by a registered dietitian. Nutrition Data System for Research software was used to determine the number of servings of fruits, vegetables and other food groups. Fasting blood samples were taken and levels of sTNF-R1 and sTNF-R2 were determined by ELISA. Logistic regression was used to determine the association between the number of servings of fruits and vegetables and sTNF-R1 and sTNF-R2 levels above the median. Differences in the number of servings of fruits, vegetables and other food groups among those with sTNF-R1 levels above and below the median were determined using independent samples t-test.

A higher consumption of vegetables but not fruits was associated with a lower risk of sTNF-R1 levels above the median after controlling for age, gender, NYHA class, diabetes, waist circumference, body mass index and energy intake (odds ratio=.84 95% CI=.72-.99). Neither the consumption of fruits nor vegetables was associated with levels of sTNF-R2. Patients with sTNF-R1 below the median consumed a greater number of servings of vegetables compared with those with sTNF-R1 levels above the median (3.44 ± 2.11 vs. 2.91± 1.78, p=.046). There were minimal differences in the consumption of other food groups between those with sTNF-R1 levels above and below the median.

The results of this study demonstrate that consumption of higher levels of vegetables is associated with lower levels of sTNF-R1 in patients with HF.

2. Introduction

Fruits and vegetables are rich sources of antioxidant vitamins and other biologically active plant compounds such as polyphenols.[1, 2] Their consumption has been

associated with decreased risk of chronic disease[3-6] and lower levels of inflammatory markers such as TNFα , interleukin-6[7] and C-reactive protein.[8-10] These associations were evident even after controlling for other variables that may influence inflammation.[7-10] The majority of studies investigating this relationship have been conducted in populations free of cardiovascular disease(CVD)[7-9] or investigators have controlled for the presence of CVD in their analyses.[10] No investigation has examined this relationship in patients with heart failure (HF).

Levels of the inflammatory cytokine TNFα[11-17] and its soluble receptors sTNF-R1 and sTNF-R2[12-14, 16] are elevated in patients with HF when compared with normal controls. TNFα may contribute to the progression of HF[18, 19] by decreasing the force of heart contraction and by contributing to cardiac remodeling.[19, 20] Furthermore, higher levels of TNFα,[21] sTNF-R1 and sTNF-R2[22, 23] are associated with poorer survival in patients with HF. Thus, identifying nutritional factors that are associated with lower levels of these inflammatory markers is of key importance, as it may provide a potential method for decreasing inflammation and improving survival. Therefore, the primary purpose of this study was to determine if higher fruit and vegetable consumption was associated with lower levels of inflammatory markers in patients with HF. In addition, because overall healthful dietary patterns have also been associated with lower levels of inflammation[24-26] it is also of interest to identify differences in other dietary patterns among those with lower and elevated inflammatory markers.

3. Methods

3.1 Sample

Two hundred twenty-one patients with HF were recruited from cardiology clinics at the University of Kentucky, Indiana University, and Emory University. To be included in the study patients had to meet the following eligibility criteria: a) documented diagnosis of HF with either preserved or non-preserved ejection fraction, b) on stable doses of their medications for three months, and c) able to read and speak English. Patients were excluded from the study due to a) HF etiology of rheumatic heart disease or pregnancy, b) obvious cognitive impairment, c) terminal illness, d) stroke or myocardial infarction in the prior three months, e) autoimmune disease, or f) end-stage renal failure.

3.2 Measurement of variables

3.2.1 Inflammatory markers

To assess proinflammatory activity of TNFα plasma levels of sTNF-R1 and sTNF-R2 were measured. The soluble TNFα receptors are cleaved from the cell membrane and released into circulation after TNFα binding. As such sTNF-R1 and sTNF-R2 are used as markers of TNFα activity.[18] Plasma levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Alpco Immunoassays) in the University of Kentucky General Clinical Research Center (GCRC) core laboratory. All samples were run in duplicate and the mean of the two measurements was used. The analysis was repeated if the coefficient of variation between the two measures was greater than ten percent.

3.2.2 Nutritional intake

Fruit and vegetable consumption, total energy (kcal) intake, kcal distribution and consumption of grains, dairy, meat, fish, and nuts were determined by four-day food diary analysis. Patients were supplied with food diaries for recording intake and digital electronic food scales. Patients were asked to weigh and record all foods and beverages that were consumed during the four day period. In addition, participants were asked to record details of food preparation methods, product brand names and recipes when possible. The diaries consisted of three weekdays and one weekend day because food consumption is typically altered on the weekends in comparison with food consumption throughout the week.[27] Additional details regarding food diaries are provided in the Procedure section (section 3.3) below.

Food diaries were analyzed using Nutrition Data System for Research (NDSR) software (NCC University of Minnesota). This software package includes nutrient data on 19,000 foods, 8,000 brand names, and 160,000 food variations that account for differences in food preparation methods. Servings of fruits and vegetables and other foods were determined using the NDSR Food Group Serving Count System. This system counts the number of servings of foods at the whole food level (e.g. whole apples, 100% fruit juice, broccoli) and at the ingredient level to capture intake of food groups contained in combination foods (e. g. casseroles, soup, lasagna). Serving sizes are based on the Dietary Guidelines for Americans 2005.[28] The number of servings of fruits, vegetables and other food groups was calculated by averaging the number of servings of these foods over the four day period. Kcal intake and kcal distribution were determined by averaging kcal intake and the percent of kcal from carbohydrate, fat

(saturated fat, monounsaturated fat and polyunsaturated fat) and protein over the four day period as well.

All vegetables with the exception of fried potatoes (e.g. French fries, hash browns) were included in the vegetable category and all fruits including 100% fruit juices were included in the fruit category. Grains were differentiated as whole or refined grains. Whole grains included all grains that were 100% whole grain or in which a whole grain was listed as the first ingredient on the label. Dairy foods were differentiated as full fat/reduced fat or low fat. Full fat and reduced fat dairy included full fat cheeses, yogurts, milk or reduced fat milk. Low fat dairy included fat free and low fat yogurts, 1% and skim milk and low fat and fat free cheeses. High fat meats were designated as fried meats and fried fish and those meats that were greater than 10% fat by weight. Lean meats were considered those that were less than 10% fat by weight and all fish except fried fish.

3.2.3 Other variables of interest

We also collected data on other variables that may influence inflammation in order to control for these in statistical analysis. Age, gender, and New York Heart Association (NYHA) functional class were determined through patient interview. Medication use was determined by patient interview and verified using the medical record. Weight and height were measured in light clothing without shoes using professional grade scales and stadiometers. From these values body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured in centimeters at the level of the iliac crest and at the end of a normal expiration. Results from our previous investigation demonstrated higher levels of inflammation in HF patients with diabetes(DM).[29] For this reason we also chose to control for DM in statistical analysis. The presence of DM was determined by patient interview and verified using the medical record.

3.3 Procedure

Approval was obtained from the Institutional Review Board at each of the sites involved in the study. After being screened for eligibility patients were approached during clinic visits, and informed written consent was obtained. Appointments at the GCRC and home visits from a research nurse were then scheduled. The research nurse visited the patient one week prior to the GCRC appointment to deliver a food diary and digital food scale. At these appointments use of the scale was explained and demonstrated. Patients were asked to give a return demonstration weighing items on the food scale and

recording in the food diary. Patients were also given pictures to help them estimate portion sizes if there were times when they were unable to weigh their food (e.g. dining at a restaurant). The research nurse called participants on the day they began their food diary to verify understanding and address problems if needed. On the morning following the last day of the food diary, patients visited the GCRC to have fasting blood drawn and height, weight and waist circumference measured. A registered dietitian reviewed all food diaries to verify serving sizes, clarify food preparation methods, and obtain additional details. At these appointments research nurses interviewed patients to determine age, gender, NYHA class, medication use and presence of DM. The medical record was used to verify medication use and the presence of DM. Plasma samples obtained at Indiana University and Emory University were shipped on dry ice to the University of Kentucky GCRC and stored at -80° C until analyzed.

3.4 Data analysis

Logistic regression was used to determine the odds ratios for sTNF-R1 and sTNF-R2 above the median. The average number of servings of fruits and the average number of servings of vegetables were entered separately into the regression model. Additional variables controlled for were age, gender, NYHA class, diabetes, BMI, waist circumference and energy intake. Differences in sample characteristics by median sTNF-R1 were determined using independent samples t-test for continuous variables and chi square for categorical variables. Sample characteristics are displayed by median sTNF-R1 because participants were divided by the median of inflammatory markers for regressions and because associations between dietary variables and inflammation were only apparent for sTNF-R1. Differences in eating patterns were determined by independent samples t-test. Predictive Analytics Software version 16.0 was used for all analyses with a $p < .05$ considered statistically significant.

4. Results

4.1 Patient characteristics

Patient characteristics are displayed in Table 4.1. Patients with sTNF-R1 values above the median were older and had a higher waist circumference than patients with sTNF-R1 values below the median. Also, a greater percentage of patients above the median had DM. This corresponds with our previous investigation in which HF patients with DM had higher levels of inflammation compared with HF patients without DM.[29] There were no other significant differences in patient characteristics between groups.

4.2 Soluble TNFα receptors and fruit and vegetable consumption

Independent predictors of sTNF-R1 and sTNF-R2 above the median are presented in Tables 4.2 and 4.3 respectively. Higher vegetable, but not fruit consumption was associated with a lower sTNF-R1 level. There was a 16 % reduction in risk of having sTNF-R1 levels above the median for every additional serving of vegetables consumed per day. A higher BMI was also associated with a lower risk, while age, being female and waist circumference were associated with a higher risk of having sTNF-R1 levels above the median. In contrast, higher vegetable intake and BMI were not associated with lower sTNF-R2 levels. Higher age and waist circumference were the only independent predictors of sTNF-R2 levels above the median.

4.3 Dietary patterns by median sTNF-R1

Dietary patterns by median sTNF-R1 are displayed in Table 4.4. Those patients with sTNF-R1 levels below the median consumed significantly more vegetables compared with patients with levels above the median. Similarly, those with sTNF-R1 levels below the median also consumed more non-lean meats (< 90% lean) compared to those above the median. There were no other differences in eating patterns between groups.

5. Discussion

This is the first study to investigate the association of fruit and vegetable consumption with levels of inflammatory markers in patients with HF. Each additional serving of vegetables was associated with a 16% reduction in risk of having sTNF-R1 levels above the median. This association was not found for fruit consumption. Neither fruit nor vegetable consumption was predictive of sTNF-R2 levels.

Prior studies have demonstrated that higher fruit and vegetable consumption is associated with lower levels of inflammation in populations without HF. Holt et al[7] investigated this relationship in 285 adolescents. After controlling for age, gender, race, energy intake and BMI, investigators found that vegetables but not fruits were inversely associated with TNFα levels. Although this study was conducted in a dissimilar population, our results are supportive of this relationship. We found that higher consumption of vegetables but not fruits was associated with a lower risk of having an elevated sTNF-R1 in patients with HF.

Several other investigations have identified that fruit and vegetable consumption is associated with other markers of inflammation, such as C-reactive protein (CRP), in non-HF populations. Gao et al[10] investigated this relationship in 599 elders. They found

that the likelihood of having an elevated CRP was 21% lower per serving of combined fruit and vegetable intake. Subsequent investigators have also demonstrated that CRP levels decrease with increasing intake of fruit[8, 9] and vegetables.[9]

In this study the association between vegetable intake and sTNF-R1 was evident even after controlling for other factors that may influence levels of inflammatory markers. Of particular interest is the inverse relationship between BMI and sTNF-R1 levels. Obese and overweight patients with HF have been demonstrated to have better survival compared with normal weight patients.[30, 31] One postulated explanation of this relationship is that overweight and obese patients may have an altered proinflammatory cytokine profile.[32] Our results support the observation that patients with higher BMI may have lower systemic inflammatory activity. However it should be noted that this inverse relationship was demonstrated after controlling for waist circumference, which was associated with higher risk, indicating the effects of higher BMI independently of abdominal obesity.

Interestingly, DM was not a significant predictor of risk for elevated sTNF-R1 or sTNF-R2 levels. This contrasts with our previous study in which higher levels of sTNF-R1 were found in overweight and obese patients with DM in comparison to overweight and obese patients without DM.[33] Higher waist circumference is indicative of greater abdominal adiposity and is associated with greater risk of type 2 DM than is adipose tissue in other regions of the body.[34] The results of this study suggest that elevated levels of sTNF-R1 in patients with DM may be due to higher waist circumference in these patients.

TNFα has both local effects on the myocardium as well as peripheral effects. It is thought to contribute to the progression of HF through its contribution to changes associated with cardiac remodeling such as apoptosis, fibrosis, and hypertrophy and through depressing myocardial contractility.[19, 20] Peripherally TNFα impairs vasodilation of tissues and may thereby contribute to the exercise intolerance characteristic of HF.[18] In addition, it is also thought to induce anorexia and muscle wasting associated with cachexia,[18] an independent predictor of mortality in patients with HF.[35] Although the two soluble receptors of TNFα, sTNF-R1 and sTNF-R2, have been associated with poorer survival in patients with HF,[22, 23] their functional roles after TNFα binding are still being clarified. While the extracellular domains of sTNF-R1 and sTNF-R2 are very similar in structure, their intracellular domains demonstrate significant heterogeneity,[36] indicating different effects for these receptors. Indeed, recent studies in murine models of HF[37] and

myocardial infarction[38] indicate that sTNF-R1 exacerbates hypertrophy and other TNFα induced cardiac remodeling processes, while sTNF-R2 ameliorates these events. These investigations underscore the importance of the association we found between higher vegetable consumption and lower levels of sTNF-R1. However, we did not find an association between vegetable consumption and sTNF-R2 levels. The reasons for this are unclear. Because TNF receptors are shed from the surface of the cell after TNFα binding, one would expect that lower levels of TNFα would translate to lower levels of both soluble TNF receptors. It is possible that these results are due to a greater variability in sTNF-R2 levels over the short-term.[39]

Fruits and vegetables may be associated with lower levels of inflammation due to their antioxidant compounds. In addition to inflammation, oxidative stress is also thought to contribute to the development and progression of HF.[40] Oxidative stress leads to the binding of the transcription factor NF-kappa B to DNA and the subsequent synthesis of proinflammatory cytokines.[41] Conversely, proinflammatory cytokines may also induce oxidative stress, creating an inflammation-oxidative stress cycle.[40] The antioxidants in fruits and vegetables may help to decrease oxidative stress by neutralizing free radicals and reactive oxygen species[42] and thereby reduce systemic inflammation. Several nutrients present in fruits and vegetables posses antioxidant properties including vitamin A, vitamin C and the carotenoids (i. e. beta carotene, lycopene, lutein, zeaxanthin).[42] Furthermore, other phytochemicals such as polyphenols not only exhibit antioxidant properties, but also demonstrate anti-inflammatory effects in in vitro studies.[42, 43] Thus fruits and vegetables contain a large number of bioactive compounds that may decrease inflammation.

In this investigation the risk of having sTNF-R1 levels above the median was 16% lower for every additional serving of vegetables consumed. It should be noted that the relationship between vegetable consumption and levels of inflammation may not be linear. Vegetable consumption may need to reach a certain threshold before decreases in sTNF-R1 levels related to vegetable consumption becomes evident. Similarly, there may also be an upper level of vegetable consumption above which additional consumption provides no benefit.

It is unclear why fruit consumption was not associated with lower levels of sTNF-R1 in this study. Both fruits and vegetables are sources of polyphenols[1] and antioxidant vitamins.[44] Although the total antioxidant capacity of several fruits and vegetables has been determined,[45] we know of no report that has determined that vegetables have a

greater antioxidant capacity than fruits. It should be noted that the consumption of fruits was relatively low (1.44 and 1.53 servings for groups below and above the median of sTNF-R1 respectively) both in this study and in the study by Holt et al[7] in which fruit consumption was not associated with TNFα levels. It is possible that the association between fruit consumption and sTNF-R1 levels does not become evident until intake reaches a certain threshold, and thus the effect of fruits on inflammation may not have been evident due to a low level of consumption.

5.1 Limitations

The prior investigators of fruit and vegetable consumption and markers of inflammation have all used food frequency questionnaires (FFQ) to assess fruit and vegetable intake.[7-10] While FFQ can provide valuable information regarding usual intake, this method relies heavily on the participant's memory and ability to accurately estimate portion sizes.[27] In contrast we used weighed four-day food diaries in which participants weighed and recorded foods as they were consumed. This method allowed us to capture detailed quantitative dietary information that was not subject to recall bias. However, although food diaries are considered representative of usual dietary intake[27] the cross-sectional design of this study limits our ability to determine causality. Further research is needed to determine if increasing vegetable consumption can lower levels of inflammation in patients with HF. Additionally, we did not control for other dietary patterns that may be associated with lower levels of inflammation. However, it should be noted that with the exception of vegetable consumption, we found minimal differences in food patterns in those above and below the median sTNF-R1 level.

6. Conclusions

The present study demonstrates that higher vegetable consumption is associated with lower levels of sTNF-R1 in patients with HF independent of other factors that may influence inflammation such as age, waist circumference, BMI, NYHA class, and DM. Due to the contribution of TNFα to the clinical manifestations and progression of HF, research investigating the benefits of lifestyle factors, such as diet, on levels of inflammation is warranted. Further research investigating the association of other dietary components with inflammation as well as the ability of increased vegetable consumption to lower levels of inflammation in patients with HF is needed.

Table 4.1 Patient characteristics

Patient characteristics	Total sample N=221	sTNF-R1 below the median n=111	sTNF-R1 above the median n=110	P value
Age	62 ± 12	59 ± 12	64 ± 11	.000
Gender, women	71 (32)	32 (29)	39 (36)	.292
NYHA				.117
I/II	134 (61)	73 (66)	61 (56)	
III/IV	87 (39)	38 (34)	49 (45)	
BMI	30 ± 8	30 ± 8	30 ± 7	.710
Waist circumference	102 ± 15	100 ± 16	105 ± 15	.021
Diabetes	74 (34)	26(23)	48 (44)	.001
ACE inhibitor	148 (69)	76 (70)	72 (68)	.776
Beta Blocker	193 (89)	97 (87)	96 (90)	.589
CLA	83 (75)	85 (77)	168 (76)	.664

Values are n(%) or mean ± standard deviation. NYHA, New York Heart Association functional class; BMI, body mass index; ACE, angiotensin converting enzyme; CLA, cholesterol lowering agent

Table 4.2 Adjusted odds ratios for sTNF-R1 above the median

Variable	Beta	Odds ratio	95% Confidence interval		P value
Age	0.04	1.04	1.01	1.07	.003
Gender	1.42	4.14	1.69	10.13	.002
NYHA III/IV	0.43	1.54	0.83	2.88	.173
Diabetes	0.64	1.89	0.98	3.64	.058
BMI	-0.13	0.88	0.80	0.97	.01
Waist circumference	0.08	1.09	1.04	1.14	.000
Kcal	0.00	1.00	0.99	1.00	.553
Fruits	0.08	1.08	0.89	1.33	.439
Vegetables	-0.17	0.84	0.72	0.99	.039

NYHA, New York Heart Association functional class; BMI, body mass index; Kcal, energy in kilocalories

Table 4.3 Adjusted odds ratios for sTNF-R2 above the median

Variable	Beta	Odds ratio	95% Confidence interval		P value
Age	0.04	1.04	1.01	1.06	.009
Gender	0.54	1.72	0.79	3.72	.171
NYHA III/IV	0.31	1.36	0.76	2.46	.303
Diabetes	0.31	1.36	0.72	2.54	.341
BMI	-0.05	0.96	0.88	1.03	.249
Waist circumference	0.05	1.05	1.01	1.09	.014
Kcal	0.00	1.00	0.99	1.00	.584
Fruits	-0.10	0.90	0.75	1.09	.299
Vegetables	-0.03	0.97	0.84	1.12	.678

NYHA, New York Heart Association functional class; BMI, body mass index; Kcal, energy in kilocalories

Table 4.4 Dietary intake by median sTNF-R1 level

	sTNF-R1 below the median	sTNF-R1 above the median	P value
Carbohydrate (% kcal)	47.56 ± 9.23	47.53 ± 8.53	0.975
Fat (% kcal)	35.29 ± 7.49	35.49 ± 7.58	0.843
Saturated fat	11.28 ± 2.8	11.79 ± 3.01	0.199
MUFA	13.69 ± 3.47	13.59 ± 3.55	0.844
PUFA	7.32 ± 2.2	7.03 ± 2.32	0.336
Protein (% kcal)	17.32 ± 4.13	17.60 ± 4.43	0.632
Vegetables	3.44 ± 2.11	2.91 ± 1.78	0.046
Fruits	1.44 ± 1.46	1.53 ± 1.64	0.669
Grains	5.06 ± 2.32	4.55 ± 2.20	0.091
Refined grains	3.87 ± 2.30	3.57 ± 1.95	0.308
Whole grains	1.38 ± 1.54	1.08 ± 1.41	0.134
Dairy	1.03 ± 0.99	1.14 ± 0.96	0.407
RF and FF dairy	0.73 ± 0.82	0.73 ± 0.64	0.986
Low fat dairy	0.28 ± 0.63	0.40 ± 0.85	0.229
Meat and fish	6.32 ± 3.62	5.45 ± 3.0	0.051
HF meat	3.21 ± 2.87	2.48 ± 2.37	0.04
Lean meat and fish	2.62 ± 1.89	2.44 ± 2.07	0.507
Nuts and seeds	0.50 ± 1.41	0.52 ± 1.23	0.935

Values are mean ± standard deviation. Kcal, energy in kilocalories; MUFA, monounsaturated fat; PUFA, polyunsaturated fat; RF, reduced fat; FF, full fat; HF, high fat

CHAPTER FIVE:
Conclusion

1. Purpose

The purposes of this dissertation were to a) determine the impact of diabetes (DM) on event-free survival of overweight and obese patients with heart failure (HF), b) explore potential inflammatory related mechanisms underlying differences in survival of normal weight, overweight and obese HF patients with and without DM and c) examine the association between levels of inflammation and fruit and vegetable consumption in patients with HF. To address these purposes three investigations were conducted. This chapter is a summary of each investigation, a description of how the results advance the current state of the science, and a discussion of implications for future research.

2. Chapter Two

Overweight and obesity were associated with increased risk for development of heart failure (HF). [1] A number of studies indicated that overweight and obesity were associated with improved survival in patients with established HF.[2-9] These seemingly conflicting relationships were suggested as a reason for the lack of consensus among current HF management guidelines. Two major limitations were identified that may contribute to the lack of a guideline consensus. First, the impact of DM on survival of overweight and obese patients has not been described. Prior investigators controlled for DM in survival analysis,[2, 3, 5-7] and thus their results demonstrated the impact of overweight and obesity independent of DM. Second, prior investigators only considered all cause or cardiac related death[3-5, 8, 9] while largely ignoring all cause hospitalization and death. The investigators who examined all cause hospitalization and death controlled for the presence of DM in the analyses.[2, 6, 7]

The investigation presented in Chapter Two addressed these limitations by comparing risk of all cause hospitalization and death of normal weight patients without DM to overweight and obese HF patients with and without DM. A total of 338 patients were recruited from three HF clinics and followed for a mean of 389 days. All cause hospitalization and death were determined through patient interview and medical record review. In contrast to prior studies in which overweight and obesity were associated with better survival,[2-9] the results of this investigation demonstrated that in the presence of DM, overweight and obese patients with HF had worse event-free survival compared with normal weight HF patients without DM. In addition, we demonstrated that when all cause hospitalization and death were considered, overweight patients without DM had

worse survival compared with normal weight patients. Using this endpoint also demonstrated that obese patients without DM had similar survival compared with normal weight patients, indicating that obesity did not confer greater risk.

There are several important implications that can be drawn from this investigation. First, the impact of obesity associated comorbidities needs to be considered, rather than controlled for in statistical analyses. Controlling for DM demonstrates event-free survival of overweight and obese HF patients independent of DM and consequently does not identify the impact of this comorbidity on event-free survival of overweight and obese patients. Second, the use of all cause hospitalization and death in survival analyses provides a better understanding of the effect of obesity on health outcomes of patients with HF because overweight, obesity[10-12] and DM[13, 14] contribute to both cardiovascular and non-cardiovascular morbidity[12, 14] and mortality.[10, 11, 13, 14] Our data provide additional clarity regarding obesity in HF and will assist with development of body weight guidelines for overweight and obese patients with HF.

Third, our data highlight the importance of managing comorbidities, which are an under-recognized component of HF care, particularly within the guidelines. Recommendations for HF patients with DM primarily focus on the use of thiazolidineiones and the safety of medications typically used for the treatment of HF (i.e. angiotensin converting enzyme inhibitors, beta blockers, angiotensin receptor blockers) with minimal guidance on optimizing care of both comorbidities.[15-17] To better inform these guidelines and to improve survival of overweight and obese HF patients with DM additional research investigating the causes of hospitalization in this patient group is needed. Although the causes of HF-related hospitalization in the general HF population have been described,[18, 19] the causes of non-HF related hospitalization in HF patients with DM have not been investigated. Identification of these causes provides an understanding of the impact of DM on all aspects of patient health—not just HF-related outcomes. Investigating these causes will also guide interventions designed to decrease hospital admissions in HF patients with DM and inform guidelines for the care of HF patients with DM as a comorbidity.

3. Chapter Three

Higher levels of inflammation were proposed as a contributor to the worse event free survival of overweight and obese HF patients with DM demonstrated in Chapter Two. Prior studies demonstrated higher levels of TNFα in patients with HF compared with normal controls.[20-24] Similarly, previous investigators demonstrated higher levels of

TNFα in patients with DM compared to individuals without DM.[25-28] In Chapter Three it was identified that prior studies were limited because investigators that examined levels of TNFα in patients with HF did not compare levels among HF patients with and without DM. Similarly, those studies in which TNFα levels were measured in people with DM did not include patients with HF. Thus, prior to this investigation, it was unknown if HF patients with DM have higher levels of inflammatory markers compared with HF patients without DM.

In the study reported in Chapter Three we addressed this knowledge gap by comparing levels of soluble TNFα receptors-1 and -2 (sTNF-R1 and sTNF-R2) in normal weight, overweight and obese HF patients with and without DM. A total of 343 patients with HF were recruited from HF clinics and stratified by body mass index and the presence or absence of DM. Fasting plasma levels of sTNF-R1 and sTNF-R2 were measured in all patients. Obese patients with DM had higher levels of sTNF-R1 compared with all non-DM groups. Overweight patients with DM had higher levels of sTNF-R1 compared with overweight and obese HF patients without DM, but there were no significant differences compared with normal weight patients. The same differences were not apparent for sTNF-R2. Although obese patients with DM had higher levels of sTNF-R2 compared with obese and overweight patients without DM, this group did not have higher levels compared with normal weight patients. Overweight patients with DM did not demonstrate higher levels compared with any group.

The results of this study advance the state of the science by demonstrating that HF patients with DM have higher levels of inflammatory markers compared with HF patients without DM, identifying a potentially modifiable factor for improving survival in HF patients with DM. Prior to this investigation, this relationship had not been examined. Further, the results of this study identify higher levels of inflammation as a potential contributor to worse survival in obese HF patients with DM. However, overweight patients with DM did not demonstrate higher levels of any inflammatory marker in comparison with normal weight patients. Consequently, whether or not inflammation is contributing to worse survival in overweight patients with DM cannot be determined from this investigation. The overweight group with DM was the smallest group with only 36 patients compared with 52, 63, 100 and 92 patients in the normal weight, overweight non-DM, obese non-DM and obese DM groups respectively. Thus this study may have been underpowered to detect significant differences in levels of sTNF-R1 and sTNF-R2

in overweight patients with DM. Further studies with larger sample sizes are needed to confirm the differences in soluble receptors demonstrated in this investigation.

Measures of blood glucose control, such as hemoglobin A1c were not determined in this investigation. Thus, the association between blood glucose control and levels of inflammation in overweight and obese HF patients with DM is unknown. Future research investigating this and the effect of lifestyle interventions designed to improve blood glucose control on levels of inflammation is needed.

4. Chapter Four

In Chapter Four we proposed that higher consumption of fruits and vegetables would be associated with lower levels of inflammation in patients with HF, potentially due to the antioxidant compounds in fruits and vegetables. In prior studies the consumption of higher levels of fruits[29-32] and vegetables[29, 30, 32] was associated with lower levels of inflammation in non-HF populations. This relationship was previously demonstrated for TNFα[32] and other markers of inflammation including interleukin-6[32] and C-reactive protein.[29-31] Prior to our study however, the relationship between fruit and vegetable consumption and levels of inflammation had not been investigated in patients with HF.

We addressed this gap in the available evidence by testing the association between fruit and vegetable consumption and levels of sTNF-R1 and sTNF-R2 in patients with HF. A total of 221 patients were recruited from HF clinics. All patients were given digital electronic food scales and asked to weigh and record all foods and beverages consumed over a four-day period. The consumption of fruits and vegetables was determined by taking the average consumption over the four day period. After controlling for age, gender, New York Heart Association functional class, DM, body mass index, waist circumference, and energy intake, higher vegetable but not fruit consumption was associated with lower risk of elevated sTNF-R1 levels. For every additional serving of vegetables, the risk of having sTNF-R1 levels above the median decreased by 16%. However, neither fruit nor vegetable consumption was associated with levels of sTNF-R2. These results suggest that vegetable consumption is associated with lower levels of sTNF-R1 in patients with HF even after controlling for other factors that may influence inflammation, such as body composition. A low consumption of fruit among all patients may explain why fruit consumption was not associated with markers of inflammation. Further, a greater variability in sTNF-R2 levels[33] may explain the lack of association between this inflammatory marker and vegetable consumption.

Our results advance the state of the science by identifying a potentially simple way to lower inflammation in patients with HF. TNFα plays a significant role in the progression of HF,[34] and a modifiable nutrition-related method of lowering inflammation could lead to improvements in survival of patients with HF. However, due to the cross-sectional design of this study, we cannot determine causality. Research testing whether increasing vegetable consumption lowers levels of inflammation in patients with HF is needed before a definitive recommendation can be made. Additional studies are also needed to determine if other food groups and an overall healthy diet are associated with levels of inflammatory markers.

5. Conclusion

Prior to these studies there were several gaps in the available evidence regarding the impact of DM on event-free survival of overweight and obese patients with HF, levels of inflammation in HF patients with DM, and the association between fruit and vegetable consumption and levels of inflammatory markers in patients with HF. This dissertation advanced the state of the science by a) identifying the impact of DM on all cause hospitalization and death in overweight and obese patients with HF and consequently clarifying the obesity paradox b) identifying higher levels of inflammatory markers as a potential contributor to poorer survival of HF patients with DM and c) demonstrating that higher vegetable consumption is associated with lower levels of inflammation in patients with HF. Additional research investigating the causes of hospitalization in HF patients with DM, the association of blood glucose control and healthful dietary patterns with levels of inflammation and the ability of improvements in blood glucose control and increased vegetable consumption to lower levels of inflammation in patients with HF is needed.

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