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Lycopene Dietary Intervention: A Pilot Study in Patients with Heart Failure

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Introduction

Heart failure (HF) is recognized as a significant contributor to cardiovascular mortality and morbidity rates in North America and most Western civilizations and is considered one of the most problematic threats to healthcare. HF is commonly a result of ischemic heart disease or hypertension. Despite advances in the treatment of HF, the mortality and hospitalization rates for HF in the USA continue to be very alarming for all healthcare entities.¹⁻⁵ Over 800,000 hospitalization visits are reported annually by Medicare and these visits consume the majority of healthcare dollars required to care for patients with HF.^{2, 6}

The connection between increased antioxidant intake and reduced cardiovascular disease (CVD) risk has been demonstrated in epidemiologic and observational studies.⁷⁻¹⁰ HF has a major inflammatory component and ischemic cardiovascular disease is the most common cause of HF.¹¹ The connection between inflammatory pathways and disease progression of HF has been supported by studies reporting elevated plasma cytokines found in patients in various stages of HF.^{12, 13} Few investigators though have examined the various stages of HF and levels of inflammation or the potential impact of increased antioxidant intake in improving outcomes in HF patients.

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There is evidence to indicate that antioxidants play a role in reducing the inflammatory process.^{14–16} Reactive oxygen and nitrogen species in high levels in the plasma is thought to be one of the contributing factors to cardiovascular disease because of the oxidation of lipids and damage to the endothelium of the vasculature.^{17–20} Increased amounts of reactive oxygen species in the myocardium can be caused by increased inflammatory cytokines or by an impairment of antioxidant production. Increased antioxidant plasma levels established in connection with fruit and vegetable intake has been found to be both inversely related to HF incidence and demonstrates a lower risk of events related to HF.^{21, 22} Lycopene is a superior antioxidant found in raw and processed food products and is considered to be one of the most efficient antioxidant at reducing reactive oxygen species, also known as free radicals.^{23, 24} Oxidative stress occurs when there is a state of imbalance between free radicals and endogenous antioxidants.¹⁹ Given the role of inflammation in HF, a novel strategy for preventing or delaying the complications of HF may be to increase lycopene intake in the diet. Supplementation with antioxidants, usually in pill form, but separate from the whole food matrix, has not been shown to be effective in many trials.^{25, 26} Thus, the purpose of this randomized, controlled pilot study was to test the effect of an intervention consisting of intake of a whole food product concentrated with lycopene on biomarkers of inflammation in patients with HF.

Our first objective was to compare the serum levels C-reactive protein (CRP) in two groups of patients with HF. The first group (intervention) consumed 11.5 ounces of V8® 100% Low-Sodium Vegetable juice (V8 juice) daily and was compared to a second group (control) of HF patients who did not consume V8 juice daily. B-type natriuretic peptide (BNP) was used as a surrogate for HF severity.^{27, 28} Our second objective was to test adherence to the intervention by comparing plasma levels of lycopene in the intervention versus control groups. Finally, we determined the impact of consumption of 11.5 ounces of V8 juice daily on sodium intake.

Methods

Study Design

This study was a two-group, randomized controlled intervention pilot study in which patients were randomized to either an intervention group (n=22) or usual care/control group (n=18). Patients were recruited from outpatient and inpatient healthcare settings in Central Kentucky. The intervention group was given one 11.5 ounce can of V8 juice to drink each day for 30 days while consuming their normal diet. The usual care group continued to consume their normal diet. Data collection included sociodemographic and clinical information, random 24 hour dietary food recalls, and blood samples for levels of uric acid, CRP, BNP and lycopene.

Sample and Setting

Eligibility criteria for patients in this study included: 1) confirmed diagnosis of HF, with preserved or non-preserved ejection fraction; 2) hospitalized for HF within the last 6 months; 3) ability to read and write English; 4) living independently (i.e., not institutionalized). Patients were excluded from the study if they: 1) were younger than 21

years of age; 2) had end stage renal disease, a co-morbidity with a known inflammatory component, or a disease or illness that was predicted to cause death within the next 12 months; 3) had impaired cognition; or 4) disliked V8 juice. Forty-three patients were invited to participate in the study. Three declined to participate due to time constraints. No patients withdrew or were lost to follow-up during the one month time frame. The final sample size was 40 patients (23 male, 17 female). (Figure 1).

Measurement

Plasma Lycopene

Plasma lycopene was obtained from venous blood (approximately 5mL) that was drawn via needle and syringe from the lower forearm into purple top EDTA vacutainer tubes (Fisher Scientific, Pittsburg, PA). Plasma was immediately separated from red blood cells by centrifuging at $1000 \times g$ at 4°C for 10 min. Blood plasma was then placed into cryovials and stored at -80°C until extraction and high performance liquid chromatography (HPLC) analysis.

Lycopene extraction—Plasma (0.5mL) was mixed with 0.5mL ethanol containing 0.1% butylated hydroxytoluene and 2.5mL of HEAT (10 hexane/6 ethanol/7 acetone/7 toluene). The mixture was probe sonicated, vortexed, and then centrifuged for 5 min at $600 \times g$. The upper non-polar layer was removed and the remaining aqueous plasma mixture was extracted twice more with 2.5 mL of HEAT. The three non-polar extracts were combined and dried under nitrogen gas. The dried extract was stored at -80°C until HPLC-PDA analysis.

C-Reactive Protein

C-reactive protein was measured using point-of-care methodology (Cholestech LDX Diagnostics, Inverness Medical Innovations). Serum was removed from the vacutainer using a pipette; 0.4ml was placed onto the Cholestech hsCRP cartridge, then placed into the Cholestech LDX® analyser. The Cholestech LDX® system uses reflectance photometry. This method of determining CRP levels has been demonstrated to provide reproducible, accurate, and valid results.²⁹

B-type Natriuretic Peptide

B-type natriuretic peptide was measured using a point-of-care machine. Serum was removed from the vacutainer tube using a pipette; 0.1ml was placed onto the Triage BNP cartridge, then into the Triage BNP® analysis machine (Biosite Diagnostics, Inverness Medical Innovations). This method of determining BNP levels has been demonstrated to provide reproducible, accurate and valid results.³⁰

Dietary intake assessment

Dietary nutrient intake was assessed using a 24-hour diet recall method to determine (1) free living intake of lycopene, and (2) sodium intake, as processed foods containing lycopene are often high in sodium. Serving size estimation charts were provided to assist with accuracy in conducting dietary recalls. This data was collected at baseline and then randomly once a

week for 3 weeks, for a total of 4 recalls for each patient. The information was recorded and analyzed using Nutrition Data System (NDS) software (NCC, University of Minnesota)³¹. The NDS software provides output for 126 nutrient and nutrient ratios from the food intake data. The database, which is updated twice yearly, contains ingredient information for over 19,000 foods including over 8000 brand name and many ethnic foods³¹.

Research Procedures

The Institutional Review Board at the University of Kentucky granted permission to conduct this study. Data about medications and supplements was obtained from the patient and verified through a review of the medical record. The patients' New York Heart Association (NYHA) functional class was determined by the research nurse. The patient interview and questionnaires were completed at the baseline visit and again at the post-intervention visit one month later.

Intervention

Patients were randomized using a computer generated random number/block chart. Patients randomized to the intervention group received a month's supply of V8 juice (30 cans). Patients were instructed that the entire can of juice could be consumed at one time or at separate times as long as the entire can was consumed each day. Each 11.5 ounce portion of V8 juice contains the following: 29.4 mg of lycopene; 70 calories; 140 mg of sodium; vitamins A and C; 820 mg of potassium; 2% of the recommended daily allowance for iron and magnesium; and 3 grams of fiber. This product contains a variety of vegetable juices (i.e., tomato, carrot, celery, beet, parsley, lettuce, watercress, and spinach)³².

Statistical Analysis

All data analyses were conducted using SPSS version 17.0 and a *P* value of < 0.05 was considered statistically significant. Descriptive analyses are presented as frequencies and means $\pm$ standard deviations as appropriate to the level of measurement of the variables. To compare baseline differences in sociodemographic and clinical characteristics between the two treatment groups, *t*-tests or chi-square were used. Intention to treat principles were applied to all data analysis. First, repeated measures ANCOVA was used to assess whether the changes over time in the outcome measures differed between the intervention and control groups, controlling for BNP level. Then, multifactorial repeated measures ANCOVA was used to evaluate whether gender or BNP interacted with group to produce a differential impact on CRP and uric acid levels.

Results

Patient Characteristics

Characteristics of the total group and of the 2 groups comparison are displayed in Table 1. A total of 40 patients who were all categorized as NYHA class II or III were enrolled. Most patients had an ischemic HF etiology. There were no significant differences between patients in the control group or the intervention group with respect to age, gender, body mass index, HF etiology, NYHA classification, medications prescribed, and smoking history or exercise patterns (Table 1). All patients who enrolled in the study completed the study.

There was only one side effect reported in relation to drinking V8 juice by 1 patient, and that was an increase in bowel movements.

Based on repeated measures ANCOVA, there were no differences between the intervention and control group in uric acid, BNP, CRP or sodium at baseline or across time (Table 2 and 3). Based on multifactorial repeated measures ANCOVA, there was a gender/intervention effect on CRP ($p=0.024$) that was not influenced by BNP. Specifically, CRP levels only decreased among women in the intervention group and not men (Table 2). There was no gender effect on uric acid levels. There was no change in CRP levels among men in the intervention group, but there was a decrease across time in the control group.

In order to explore potential reasons for the gender difference in the impact of the intervention, we compared men and women on baseline BMI and CRP levels. There were no differences between women and men in BMI (31.9 ± 9.7 vs. 30.7 ± 6.7 , respectively; $p = 0.638$). There were differences in CRP levels between women and men (5.69 ± 3.5 vs. 2.86 ± 2.62 , respectively; $p = 0.01$).

Plasma lycopene levels increased significantly in the intervention group compared to the control group ($p = 0.02$). Plasma lycopene levels changed similarly between men and women in the intervention group ($p=0.37$). There was no significant group by time interaction on sodium intake ($p = 0.237$; Table 3).

Discussion

This is the first study in which an intervention of a lycopene rich food source has been tested in a sample of patients with HF. To date, there have been two other studies in which the role of antioxidants in patients with HF has been studied. In both studies, there was a positive association between plasma lycopene levels and HF, both of these studies were observational^{33, 34}.

In our study, we found a differential effect of gender in the effect of the intervention on CRP levels. In women, the intervention resulted in a significant decrease in CRP across time, but not in men.

There are three potential explanations for our finding of a gender effect in the intervention. The possibilities include (1) greater compliance to the intervention in women than in men, (2) the effect of BMI and adiposity, and (3) the higher baseline CRP levels seen in women. With regard to the first potential explanation, there is published evidence that women are more adherent to prescribed HF regimens than men.³⁵ There was, however, no evidence in our sample that women were more compliant to the intervention than men. Lycopene levels increased significantly in both genders in the intervention group over time, while remaining unchanged in both genders in the control group.

With regard to the second potential explanation for our findings, adipose tissue produces inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, which contribute to atherosclerosis. IL-6 enhances liver production of CRP. Levels of inflammatory markers in obese persons ($BMI \geq 30 \text{ kg/m}^2$) are considered independent

predictors of CVD. Abdominal adiposity has been associated with risk of CVD in women^{36, 37}. Higher waist-hip-ratio (WHR) and greater waist circumference have been found to be independently associated with a significantly increased age-adjusted risk of CVD and HF.^{36, 38, 39} In the Nurses' Health Study, women with a WHR of 0.88 or higher had a relative risk (RR) of 3.25 (95% confidence interval, 1.78–5.95) for CVD compared with women with a WHR of less than 0.72.³⁶ There was no gender difference in BMI level in our sample of patients. However, we did not measure abdominal adiposity. This additional measurement may have shed additional light onto our findings.

With regard to the third potential explanation for our findings, women may have higher baseline levels of CRP than men.⁴⁰ For example, women participants enrolled in the Women's Health Study had a median CRP level of 0.42mg/dL compared with 0.28mg/dL in men.⁴¹ In our sample, women had significantly higher baseline CRP levels than men. Often, the effect of a variety of interventions (e.g., cardiac rehabilitation, weight loss, intake of healthy foods) is greater in those in whom the outcome of interest is most negatively affected. That is, those who have the most to gain (or lose), often show the largest effect of an intervention, at least initially.^{42–47} Thus, it is plausible that the substantially higher levels of CRP seen in the women in our study allowed the intervention to better exert its effect.

There is sufficient evidence to support that CRP plays a direct role in inflammation.⁴⁸ The fact that our study found CRP levels decreased in response to a dietary intervention is a positive finding. Any decrease in CRP levels, such as the one observed in our study, has the ability to reduce the risk of further cardiac events and is considered to be of important value to clinicians and patients.^{40, 49} A CRP in the highest quartile >0.73 mg/dL of 28,263 healthy women in a case control study had a five times greater risk of developing an acute myocardial infarction or stroke compared to those in the lowest quartile.⁴¹ CRP levels have also been shown to predict mortality in patients with dilated cardiomyopathy and to have an inverse association with left ventricular function in patients with HF.^{50, 51} If CRP levels are increased in patients affected by HF, they will further increase with the severity of the pathology and be associated with a higher rate of mortality independently of any ischemic cause.^{51, 52}

Our data also indicate that increased consumption of lycopene-containing food products results in increased plasma levels of lycopene. These data support previous studies where increased dietary intake of lycopene is reflected in increased circulating lycopene levels in plasma^{53–55}. Compliance to the V8 juice intervention was observed in both women and men in our study.

Processed foods containing high levels of lycopene also contain high levels of sodium. Approximately 80% of the sodium in the average American diet comes from processed foods. Dietary sodium indiscretion is considered to be a precipitant in >20% of patients hospitalized for decompensated HF, and high sodium intake is an independent risk factor for HF exacerbation.^{56–58} Data from an earlier investigation of ours suggest that foods containing high levels of lycopene may be beneficial regardless of its sodium content.⁵⁹ The findings of the current study did not indicate a significant increase in sodium levels after the intervention.

An important challenge in translating these findings into clinical treatment strategies relates to the fact that most clinical studies have been designed on top of established pharmacological therapy, whereas most experimental studies test novel interventions without concomitant drug regimens such as ACE inhibitors or beta-blockers. Our study tested a randomized intervention on top of evidence-based drug regimens for patients with HF and found an impact of a dietary intervention. We cannot attribute the intervention effect solely to lycopene as V8 juice does contain a variety of antioxidants and vitamins. However, V8 juice does contain a large amount of lycopene, nearly 4 times the reported average amount found in the daily intake for individuals in the United States.

With regards to the feasibility of this study of a dietary intervention, we found that patients with HF were able to adhere to the intervention, as evidenced by a compliance rate of 100%. The V8 juice cost less than \$1.00 per serving and is readily available in most urban and rural grocery stores. The patients did not report any ill effects from drinking the lycopene product for 30 days. This intervention was easily implemented by a sample of patients with difficult self-care regimens.

In addition to establishing feasibility, the study has strength in the two group randomization of participants. Secondly, we were able to obtain valuable detailed nutritional information from the participants via randomly collected dietary 24 hour recalls at multiple time points. There are several limitations to this study. Due to the small sample size, it is difficult to generalize to entire population of people with HF. Additional biomarkers of inflammation, such as inflammatory cytokines could be measured in conjunction with CRP to further elucidate the impact of inflammation in HF. The gender differential we found warrants further investigation as well.

Conclusion

The study of the role of dietary antioxidants as interventions for inflammation in patients with HF is novel. To date, investigators have largely studied supplements as sources of micronutrients. Lycopene is a natural plant compound found in fruits and vegetables. Lycopene-containing products are inexpensive, readily available, shelf-stable, and versatile. In a sample of patients with HF who received a lycopene rich dietary product, we found a significant increase in plasma lycopene levels. Serum CRP levels, as a biomarker of inflammation, did not decrease in the intervention group as a whole, but levels significantly decreased within the female gender group. These findings suggest the naturally occurring antioxidant lycopene interacts with gender to affect CRP levels in a sample of patients with HF. Although a physiologic mechanism is unclear, additional studies will help clarify this finding. This study provides insight to the potential role of antioxidants, like lycopene in HF and may lead to additional treatment strategies. These findings are a preliminary step in a process of establishing efficacy of a specific dietary intervention with antioxidants that may have a clinically significant effect on inflammation in patients with HF.

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Abbreviations

HF	heart failure
μmol/L	micromoles per liter
CVD	cardiovascular disease
CRP	c reactive protein
BNP	brain natriuretic peptide
ml	milliliters
EDTA	ethylenediaminetetraacetic acid
HPLC	high performance liquid chromatography
NYHA	New York Heart Association functional classification
ANCOVA	analysis of covariance
BMI	body mass index
ROS	reactive oxygen species

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What's New and Important?

- The antioxidant lycopene found in V8 100% vegetable juice affects inflammation as measured by CRP levels in a sample of female patients with heart failure.
- Lycopene is a natural phytochemical found in fruits and vegetables. Lycopene-containing products are inexpensive, readily available, shelf-stable, and easily incorporated into a heart healthy diet.

Figure 1.
CONSORT Flow Diagram

Table 1

Patient Characteristics

Characteristics	N (%) or Mean $\pm$ SD			
	Total (n = 40)	Intervention (n= 22)	Control (n= 18)	P value
Age (years)	65 $\pm$ 9	65 $\pm$ 11	65 $\pm$ 9	.999
Gender				
Male	23	8 (35)	15(65)	.131
Female	17	10 (59)	7 (41)	
Body mass index (kg/m ²)	31 $\pm$ 8	30 $\pm$ 5	32 $\pm$ 9	.257
NYHA class				
II	28 (70)	16 (57)	12 (43)	.677
III	12(30)	6 (50)	6 (50)	
Heart failure etiology				
Non-ischemic	6 (15)	5 (83)	1 (17)	.130
Ischemic	40 (85)	17(50)	17 (50)	
Medication				
ACE inhibitors	35 (88)	16 (46)	19 (54)	.987
β blocker	30 (75)	17 (57)	13 (43)	
Diuretics	19 (48)	9 (47)	10 (53)	
Smoking History				
Current	8 (20)	4(50)	4(50)	.935
Former	20 (50)	11(55)	9 (45)	
Never	12/40 (30)	6 (50)	6 (50)	
Exercise frequency				
< 1 hour/week	21/40 (53)	11(52)	10 (48)	.726
1 hour/week	19/40 (47)	11 (58)	8 (42)	
BNP Levels, pg/ml				
Baseline	167 $\pm$ 198	196 $\pm$ 237	132 $\pm$ 133	.316

Table 2

Serum C - reactive protein and Uric Acid Pre- and Post-Intervention Compared between the Groups Using B-type Natriuretic Peptide as a Covariate

	C-reactive Protein mg/L [*] ± SD		Uric Acid mg/dl [*] ± SD	
	Intervention	Control	Intervention	Control
Baseline	3.4 ± 3.1	4.8 ± 3.4	7.2 ± 1.5	7.2 ± 2.3
Post-Intervention	3.1 ± 2.8	4.5 ± 3.8	7.2 ± 1.3	7.3 ± 2.5

Legend: Post-intervention was 30 days after baseline;

*
p > 0.05 for time and group effect; SD= standard deviation

Table 3

Sodium Levels by Dietary Intake

	Sodium intake* $\pm$ SD		
	Total	Intervention	Control
Baseline	2671 $\pm$ 1252	2858 $\pm$ 1389	2443 $\pm$ 1055
Post-Intervention	2864 $\pm$ 1036	3182 $\pm$ 1063	2474 $\pm$ 879

Legend: Sodium = mg/day; Post-intervention was 30 days after baseline;

* $p > 0.05$ for time and group effect; SD= standard deviation