Healthy diet reduces markers of cardiac injury and inflammation regardless of macronutrients: Results from the OmniHeart trial

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ABSTRACT

Background: Despite diet being a first-line strategy for preventing cardiovascular disease, the optimal macronutrient profile remains unclear. We studied the effects of macronutrient profile on subclinical cardiovascular injury and inflammation.

Methods: OmniHeart was a randomized 3-period, crossover feeding study in 164 adults with high blood pressure or hypertension (SBP 120–159 or DBP 80–99 mm Hg). Participants were fed each of 3 diets (emphasizing carbohydrate (CARB), protein (PROT), or unsaturated fat (UNSAT)) for 6-weeks, with feeding periods separated by a washout period. Weight was held constant. Fasting serum was collected at baseline while participants ate their own diets and after each feeding period. High-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity C-reactive protein (hs-CRP) were measured in stored specimens.

Results: The average age was 53.6 years, 55% were African American, and 45% were women. At baseline, the median (25th-percentile, 75th-percentile) hs-cTnI was 3.3 ng/l (1.9, 5.6) and hs-CRP was 2.2 mg/l (1.1, 5.2). Compared to baseline, all 3 diets reduced hs-cTnI: CARB –8.6% (95%CI: −16.1, −0.4), PROT –10.8% (−18.4, –2.5), and UNSAT –9.4% (−17.4, −0.5). Hs-CRP was similarly changed by −13.9 to −17.0%. hs-CttnI and hs-CRP reductions were of similar magnitudes as SBP and low-density lipoprotein cholesterol (LDLc) but were not associated with these risk-factor reductions (P-values = 0.09). There were no between-diet differences in hs-cTnI and hs-CRP reductions.

Conclusions: Healthy diet, regardless of macronutrient emphasis, directly mitigated subclinical cardiac injury and inflammation in a population at risk for cardiovascular disease. These findings support dietary recommendations emphasizing healthy foods rather than any one macronutrient.

Trial Registration: This trial is registered at clinicaltrials.gov, number: NCT00051350; URL: https://clinicaltrials.gov/ct2/show/NCT00051350.

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Abbreviations: CARB, the OmniHeart carbohydrate feeding period; CI, confidence interval; CVD, cardiovascular disease; eCPR, estimated glomerular filtration rate; DBP, diastolic blood pressure; BMI, body mass index; LDLc, low-density lipoprotein cholesterol; DASH, Dietary Approaches to Stop Hypertension; GEE, generalized estimating equation; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; OmniHeart, Optimal Macronutrient Intake Trial to Prevent Heart Disease; PROT, the OmniHeart protein feeding period; SBP, systolic blood pressure; SD, standard deviation; UNSAT, the OmniHeart unsaturated fat feeding period.

1 This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussion interpretation.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States [1]. Dietary interventions play a critical role in recommendations to prevent CVD in adults [2,3] based on reported improvements in CVD risk factors [4–7]. However, there has been minimal improvement in diet quality among US adults over the past several decades [8,9]. One of the challenges facing promotion of healthy diet in the US has been conflicting recommendations for what macronutrients should be emphasized as part of a healthy diet. Some experts have emphasized high fat/low carbohydrate patterns as optimal, while others focus on low fat/high carbohydrate diets [10]. However, it is possible that the macronutrients matter less than simply eating healthy foods. In spite

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of this, there is limited evidence for whether a healthy diet might directly improve causal intermediaries of CVD, e.g. subclinical myocyte injury and inflammation [11,12] not to mention the effects of specific macronutrients on direct measures of subclinical CVD.

The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) trial was designed to examine the effects of 3 healthy diets that emphasize different macronutrients (carbohydrates, protein, or unsaturated fat) on CVD risk factors [6]. Participants were included with baseline elevated blood pressure (BP) or hypertension, but not yet on medications for BP or cholesterol [6]. All 3 OmniHeart diets showed large reductions in systolic BP (SBP) and low-density lipoprotein cholesterol (LDLc) after six-weeks, which were predicted to reduce 10-year coronary heart disease risk by 16–21% [6]. However, whether these diets had a direct impact on myocyte injury or inflammation was not reported. With the advent of assays for high-sensitivity troponin, a highly specific marker of myocardial cell injury detectable even in the ambulatory population, it is now possible to directly measure subclinical cardiac damage [13–15]. Furthermore, recent studies have re-established the importance of inflammation, reflected by high-sensitivity CRP (hs-CRP), as an independent factor associated with the development of atherosclerosis and CVD [16–18].

Using stored specimens from OmniHeart, we measured high-sensitivity cardiac troponin I (hs-cTnI) and hs-CRP to: [1] determine the effects of 3 healthy diets on hs-cTnI and hs-CRP, [2] examine whether macronutrient profile would further affect hs-cTnI and hs-CRP, and [3] study the relationship between change in hs-cTnI and hs-CRP with changes in important CVD risk factors, i.e. SBP and LDLc. We hypothesized that both hs-cTnI and hs-CRP would decrease from baseline with little difference between diets, similar to the changes in SBP and LDLc observed from baseline in the original OmniHeart trial.

2. Subjects and methods

The rationale, design, and main outcomes of the OmniHeart Trial have been reported [6,19]. In brief, OmniHeart was a two-center, investigator-initiated, feeding study with a randomized, 3-period cross-over design sponsored by the NHLBI. This trial tested the effects of 3 healthful diets, differing in macronutrient composition, on traditional CVD risk factors (BP and LDLc) in the setting of stable weight. Specimens from the original trial were maintained and curated by the NHLBI and made available by request via the BioLincc repository.

Institutional Review Boards at Johns Hopkins University, Brigham & Women’s Hospital, and the Harvard School of Public Health approved the original study protocol.

2.1. Participant recruitment

Adult men and women, residing in and around Boston, MA, and Baltimore, MD, participated in OmniHeart between April 2003 and June 2005. Participants were required to be aged ≥ 30 years with SBP 120–159 or DBP 80–99 mm Hg. Adults with a diagnosis of diabetes, kidney disease (eGFR < 60 mL/min per 1.73 m²), a prior history of CVD, >2 alcoholic drinks per day for men or >1 alcoholic drink per day for women, or use of medications for the treatment of hypertension or hyperlipidemia were excluded [6]. Of the initial 191 participants randomly assigned to 6 diet sequences, 164 completed at least 2 feeding periods. Of these, 162 had stored specimens at the time of hs-cTnI measurement, and 155 had stored specimens at the time of hs-CRP measurement (Supplemental Fig. 1).

2.2. Dietary intervention

OmniHeart included 3 healthful diets: a carbohydrate-rich diet (CARB) with 58% kilocalories from carbohydrates (similar to the DASH diet), a protein-rich diet (PROT) with 10% of kilocalories from carbohydrates replaced by protein, and an unsaturated fat-rich diet (UNSAT) with 10% of kilocalories from carbohydrate replaced by unsaturated fats (Supplemental Table 1). All 3 diets were low in saturated fat, cholesterol, and sodium (2300 mg/day), while providing other nutrients at recommended dietary levels. In the PROT diet, the food sources for protein replacement were two-thirds vegetable-based. Diets were designed using commonly available foods.

Participants were randomized to 1 of 6 dietary sequences with a 2 to 4-week wash-out period between each diet, during which participants ate their own food (Supplemental Fig. 1) [6]. Each feeding period lasted 6-weeks. Calorie targets were determined for each participant based on body size, sex, and physical activity; calorie targets were then adjusted throughout the study to keep weight within 2% of baseline. Participants were encouraged to maintain usual physical activity levels and alcohol consumption for the duration of the study. Ultimately, participants were compliant with the feeding protocol for >95% of trial-person-days, i.e. complete consumption of all study foods without any non-study foods [6].

2.3. Measurement of main outcomes: high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity C-reactive Protein (hs-CRP)

Fasting serum was collected from each participant at baseline and at the completion of each 6-week feeding period. Blood samples were allowed to clot at room temperature for 15 min, centrifuged at 2 °C, and stored at −70 °C. In 2018, hs-cTnI was measured in serum specimens at University of Maryland (Baltimore), using donated investigational Advia Centaur High Sensitivity-Cardiac Troponin I assays (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) with a range of 0.10–25,000 ng/L. Values below 0.1 ng/L were imputed as 0.05. This affected only 2 people: one participant was <0.1 ng/L at baseline and another was undetectable at baseline and each of the 3 follow-up visits. Details of assay performance have been published previously [20]. Hs-CRP was measured by nephelometric assay in 2008 (Vista Intelligent Lab System, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

2.4. Other measurements and variables

Age, sex, race (white, black, or other), ethnicity (Hispanic or non-Hispanic), current smoking status, and education were self-reported via questionnaires. Body mass index (BMI) was derived via baseline height and weight measurements. Baseline SBP and DBP were measured using the average of 3 BP assessments obtained during separate screening visits at least one week apart. Participants were considered to have stage 1 or 2 hypertension at baseline if they had an average baseline SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg. Traditional assays were used to measure total triglycerides and HDL cholesterol. LDLc levels were estimated by the Friedewald equation [21].

2.5. Statistical analysis

2.5.1. Baseline characteristics and marker distributions

Study population characteristics were described using means (SD) and proportions. Both hs-cTnI and hs-CRP were log-transformed to account for data skew. Means of log-transformed hs-cTnI and hs-CRP were examined at baseline and the end of each of the 3 feeding periods. Kernel density plots were used to compare the distributions of log-transformed hs-cTnI and hs-CRP at baseline and at the end of the 3 feeding periods.

2.5.2. Change from baseline and between diet comparisons

The primary outcomes were log-transformed hs-cTnI and log-transformed hs-CRP. The primary comparisons were % baseline change in hs-cTnI and hs-CRP, which were determined for each feeding period with linear regression, using generalized estimated equations (GEE).
With robust standard errors and exchangeable covariance structure to account for correlated measures.

End of period, log-transformed hs-cTnI and hs-CRP were also compared across diets (PROT versus CARB, UNSAT versus CARB, PROT versus UNSAT), using the GEE models above.

2.5.3. Comparison with cardiovascular disease risk factors

We examined the relationship between SBP and LDLc with hs-cTnI and hs-CRP at baseline using linear regression. Furthermore, we compared baseline and between-diet changes in hs-cTnI and hs-CRP with changes in SBP and LDLc reported in the original OmniHeart trial [6]. Linear regression, Lowess curves, and scatter plots were used to compare baseline changes in hs-cTnI or hs-CRP with baseline change in SBP or LDLc.

To understand whether there were disproportionate dietary effects among at-risk subgroups, we performed stratified analyses, based on age (≥60 years), sex, black race, hypertension (baseline SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg), obesity (≥30 kg/m²), or current smoking status. Interaction terms were used to compare effects across strata.

All analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

Demographic characteristics are provided in Table 1. Overall, the mean age was 53.5 (SD, 10.9) years, 55% were African American, and 45% were female. The mean BMI was 30.2 (SD, 6.1) kg/m², and 55% had stage 1 or 2 hypertension (SBP ≥ 130 or DBP ≥ 80 mm Hg).

3.2. Changes from baseline and end-period comparisons

At baseline, median (25th percentile, 75th percentile) hs-cTnI was 3.3 (1.9, 5.6) ng/L and median hs-CRP was 2.2 (1.1, 5.2) mg/L (Table 1). Compared to baseline, all 3 diets significantly reduced hs-cTnI and hs-CRP (Fig. 1). This was reflected by a leftward shift in the distribution of hs-cTnI and hs-CRP values (Supplemental Fig. 2). The CARB diet changed hs-cTnI by −8.6% (95% CI −16.1, −0.4; P = 0.04) and hs-CRP by −17.0% (−26.6, −6.1; P < 0.003). Similarly, the PROT diet changed hs-cTnI by −10.8% (−18.4, −2.5; P = 0.01) and hs-CRP by −13.9% (−24.9, −1.3; P = 0.03), and the UNSAT diet changed hs-cTnI by −9.4% (−17.4, −0.5; P = 0.04) and hs-CRP by −16.0% (−26.5, −4.1; P = 0.01). None of the diets differed in terms of the magnitude of hs-cTnI or hs-CRP reductions, i.e. all pairwise contrasts were non-significant (Table 2).

3.3. Comparison with risk factors

We examined the association between SBP and LDLc with hs-cTnI and hs-CRP measured at baseline (Supplemental Table 2). There was a positive association between baseline SBP and baseline hs-cTnI (P = 0.005), but not baseline hs-CRP (P = 0.09). LDLc was not significantly associated with either outcome (Supplemental Table 3). We then compared changes in hs-cTnI and hs-CRP (end of intervention minus baseline) with changes in CVD risk factors reported in the original OmniHeart trial (Table 2). The largest differences in SBP and LDLc were observed compared to baseline with reductions of 8–9 mm Hg for SBP and 11–14 mg/dL for LDLc. Differences between diets in the original study were modest (< 2 mm Hg in SBP and < 4 mg/dL for LDLc). In linear regression models, changes from baseline in SBP or LDLc were not associated with hs-cTnI and hs-CRP (Supplemental Fig. 3).

3.3.1. Stratified analysis

We examined baseline change in hs-cTnI and hs-CRP by diet in strata of age, sex, race, hypertension, obesity, and smoking status (Table 3). In black participants, the 3 healthy diets had a greater impact on hs-cTnI (−10.2 to −17.3%) compared to non-black participants (−4% to 1.3%, P = 0.04); although, no significant difference was seen for hs-CRP. Among participants without hypertension, hs-cTnI was more affected by healthy diet (−26.7 to −31.4%) than among participants with hypertension (−2.7 to −8.6%, P = 0.04).

4. Discussion

In the OmniHeart study, 3 healthy DASH-pattern diets lowered both hs-cTnI and hs-CRP over 6-weeks in participants with elevated BP or hypertension. Effects did not differ by macronutrient. While changes in hs-cTnI and hs-CRP mirrored the magnitude of the diets’ effects on SBP and LDLc, these changes were not associated with changes in SBP and LDLc. Together, these findings suggest that a healthy diet, regardless of macronutrient profile, can directly mitigate subclinical cardiac damage and inflammation beyond traditional risk factors. While stratified analyses indicated that certain subgroups may benefit more in terms of hs-cTnI and hs-CRP reduction, our results were largely consistent across groups.

Troponin is the gold-standard marker for diagnosing acute myocardial infarction (MI), as a highly specific marker of myocardial cell injury [13]. Improvements in the assay led to the development of high-sensitivity cardiac troponin T (hs-cTnT) [14]. Moreover, treatment of LDLc with pravastatin in the West of Scotland Coronary Prevention Study reduced hs-cTnI by 13% (10–15%, P < 0.001) compared to placebo over 5-years of follow-up [24]. However, whether a healthy diet could also reduce hs-cTnI has not been previously shown.

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Evidence for a causal relationship between healthy diet and the reversal of subclinical cardiac injury is scarce, and observational data has been contradictory. While some studies have shown that healthy diet in combination with other healthy lifestyle choices is associated with reductions in subclinical myocardial injury based on hs-cTnT over a 6-year period [25], others have not found an association between hs-cTnT and healthy diet [26]. Furthermore, two trials, both a dietary intervention period [25], others have not found an association between hs-cTnT and healthy diet [26]. Nevertheless, two trials, both a dietary intervention period [25], others have not found an association between hs-cTnT and healthy diet [26].

There are few studies examining the relationship between diet and hs-CRP. Observational studies have demonstrated an inverse relationship between healthy diet and hs-CRP [31–33]. Interventional studies and meta-analyses have been mixed with some showing that diet and physical activity lower hs-CRP [34,35], while others show no effect [12,36]. In a sub-study of the DASH-Sodium trial, baseline hs-cTnI strongly modified the effect of the DASH diet on LDLc levels, but the study (N = 100) was underpowered to see an effect from DASH on hs-CRP [11]. With similar diets but greater power in OmniHeart, our findings provide support for the role of diet in reducing cardiac inflammation.

This study meaningfully informs ongoing debates about the importance of macronutrient intake for cardiovascular health [10]. Recent evidence suggests that macronutrient pattern does not influence CVD risk factors [37]. In OmniHeart, the CARB diet was similar to the DASH diet, which is high in carbohydrate, while UNSAT is a version of the DASH diet that emphasizes unsaturated fat, i.e. similar to a Mediterranean-style diet [38]. However, in the primary study, the between-diet differences in SBP and LDLc were small and did not translate into significantly different effects on hs-cTnI and hs-CRP. While the long-term consequences of these small differences in CVD risk factors are unknown, in the short-term adopting any of the 3 healthy diets appeared to be more important than the macronutrient composition of any one single diet. This finding supports flexibility in food selection for individuals attempting to consume a healthful diet and should improve adherence. With only 1 in 10 US adults meeting the daily recommended fruits and vegetable intake, and the average American eating 1 serving of fruit and 2 servings of vegetables [39], the typical American diet is quite different from the OmniHeart diets, where all 3 included 4–6 servings each of fruits and vegetables per day.

Our study has limitations. First, feeding periods were 6-weeks long, and outcomes represent causal mediators of CVD rather than clinical events. While hs-cTnI and hs-CRP are strongly associated with CVD events [16,17], Exposure to hs-CRP ≥ 3 mg/L over time is associated with higher risk of CVD [29]. Furthermore, one large trial (CANTOS) demonstrated that CVD events were reduced by targeting inflammatory pathways [30]. In fact, CANTOS participants who achieved on-treatment hs-CRP < 2 mg/L had a 31% reduction in both cardiovascular and all-cause mortality compared to those with hs-CRP ≥ 2 mg/L [18].

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure, mm Hg</th>
<th>LDL cholesterol, mg/dL</th>
<th>High-sensitivity troponin I (%)</th>
<th>High-sensitivity C-reactive protein (%)</th>
<th>Estimated 10-yr CHD risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean change</td>
<td>P</td>
<td>Mean change</td>
<td>P</td>
<td>Mean % difference</td>
</tr>
<tr>
<td>CARB vs BL</td>
<td>−8.2</td>
<td>−0.01</td>
<td>−11.6</td>
<td>−0.01</td>
<td>−8.6</td>
</tr>
<tr>
<td>PROT vs BL</td>
<td>−9.5</td>
<td>−0.01</td>
<td>−14.2</td>
<td>−0.01</td>
<td>−10.8</td>
</tr>
<tr>
<td>UNSAT vs BL</td>
<td>−9.3</td>
<td>−0.01</td>
<td>−13.1</td>
<td>−0.01</td>
<td>−9.4</td>
</tr>
<tr>
<td>PROT vs CARB</td>
<td>−1.4</td>
<td>−0.01</td>
<td>−3.3</td>
<td>0.01</td>
<td>−2.4</td>
</tr>
<tr>
<td>UNSAT vs CARB</td>
<td>−1.3</td>
<td>−0.01</td>
<td>−1.5</td>
<td>0.22</td>
<td>−0.8</td>
</tr>
</tbody>
</table>

BL: baseline; CARB: carbohydrate diet; CHD: coronary heart disease; PROT: protein diet; UNSAT: unsaturated-fat diet.

*Note magnitudes for systolic blood pressure, LDL cholesterol, and estimated 10-year risk reduction in coronary heart disease were quoted from the original trial [6].

outcomes. Second, there was no control diet in OmniHeart. As a result, it is possible that the observed effects partially reflect trial participation ( Hawthorne effect) and potentially regression to the mean. However, it should be noted that the trial did not select participants based on high levels of hs-cTnI and hs-CRP, thereby minimizing the potential for regression to the mean. The stratified analysis showed some possible sub-group effects, though the differences seen between groups are more likely related to this study being underpowered to see true subgroup disparities.

Our study has several notable strengths. OmniHeart’s crossover design in a population at risk for CVD afforded a unique opportunity to evaluate the effects of a dietary intervention on biomarkers of subclinical CVD. Assessments were rigorously performed following a standardized protocol and within the same people allowing us to determine change in hs-cTnI and hs-CRP. Furthermore, OmniHeart was conducted in a diverse population, thereby enhancing generalizability. As a feeding trial, with all foods provided to participants, OmniHeart tested the biological effects of the diets without biases related to non-adherence and measurement error, typical of observational studies. Finally, assessments of hs-cTnI and hs-CRP afforded us an opportunity to examine the effects of healthy diet on pathways of CVD injury. Given the high adherence and follow-up during each of the dietary periods without weight change, our study provides strong justification and a feasible way to lower CVD risk with diet alone.

This study has important public health implications. We documented that changes in diet can reduce subclinical cardiac injury and inflammation concurrent with reductions in other CVD risk factors. These results add substantial support to the hypothesis that diet influences causal pathways of CVD - findings meaningful for population strategies for primary prevention of CVD. Clinical CVD is the culmination of years of subclinical cardiovascular injury. While the incremental impact of short-term unhealthy lifestyle may be small, its accumulated effects become clinically evident in adults often after irreversible ischemic events [40]. A healthy diet continues to be a critical strategy, not only by shifting the distribution of cardiovascular risk factors in the population [41], but also by reductions in both cardiac injury and inflammation. We believe our findings should serve to further motivate physicians to recommend and patients to adopt a healthy diet, given the benefits seen in our study.

In conclusion, consumption of a healthy diet directly lowered hs-cTnI and hs-CRP, beyond reductions in SBP and LDLc, regardless of whether they were high in carbohydrates, protein, or fat. This study provides strong support for simplified dietary recommendations that emphasize healthy foods rather than any one macronutrient as a means to reverse subclinical cardiac injury and inflammation in populations at risk for CVD.

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Data sharing
Data described in the manuscript, code book, and analytic code is publicly available upon request through the NHLBI BioLincc repository.

Declaration of Competing Interest
The authors declare that there is no conflict of interest associated with this manuscript.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.102.

References


