Weight Loss/Caloric Restriction

Left Ventricular Mass and Function With Reduced-Fat or Reduced-Carbohydrate Hypocaloric Diets in Overweight and Obese Subjects

Sven Haufe, Wolfgang Utz, Stefan Engeli, Petra Kast, Jana Böhnke, Martin Pofahl, Julius Traber, Verena Haas, Mario Hermsdorf, Anja Mählner, Andreas Busjahn, Susanne Wiesner, Christoph Otto, Heidrun Mehling, Friedrich C. Luft, Michael Boschmann, Jeanette Schulz-Menger, Jens Jordan

Abstract—In animals, carbohydrate and fat composition during dietary interventions influenced cardiac metabolism, structure, and function. Because reduced-carbohydrate and reduced-fat hypocaloric diets are commonly used in the treatment of obesity, we investigated whether these interventions differentially affect left ventricular mass, cardiac function, and blood pressure. We randomized 170 overweight and obese subjects (body mass index, 32.9 ± 4.4; range, 26.5–45.4 kg/m²) to 6-month hypocaloric diets with either reduced carbohydrate intake or reduced fat intake. We obtained cardiac MRI and ambulatory blood pressure recordings over 24 hours before and after 6 months. Ninety subjects completing the intervention period had a full cardiac MRI data set. Subjects lost 7.3 ± 4.0 kg (7.9 ± 3.8%) with reduced-carbohydrate diet and 6.2 ± 4.2 kg (6.7 ± 4.4%) with reduced-fat diet (P < 0.001 within each group; P = not significant between interventions). Caloric restriction led to similar significant decreases in left ventricular mass with low-carbohydrate diets (5.4 ± 5.4 g) or low-fat diets (5.2 ± 4.8 g; P < 0.001 within each group; P = not significant between interventions). Systolic and diastolic left ventricular function did not change with either diet. The 24-hour systolic blood pressure decreased similarly with both interventions. Body weight change (β = 0.33; P = 0.02) and percentage of ingested n-3 polyunsaturated fatty acids (β = −0.27; P = 0.03) predicted changes in left ventricular mass. In conclusion, weight loss induced by reduced-fat diets or reduced-carbohydrate diets similarly improved left ventricular mass in overweight and obese subjects over a 6-month period. However, n-3 polyunsaturated fatty acid ingestion may have an independent beneficial effect on left ventricular mass. (Hypertension. 2012;59:70-75.) • Online Data Supplement

Key Words: ambulatory blood pressure ● cardiac function ● low-carbohydrate diet ● low-fat diet ● polyunsaturated fatty acids ● weight loss

Obesity is associated with increased left ventricular (LV) mass,1,2 a potential contributor to heart failure, cardiovascular events, and mortality.3,4 Energy-restricted diets decrease LV mass in conjunction with body weight loss.5–7 In addition to caloric intake, dietary macronutrient composition appears to influence cardiac metabolism, structure, and function,8 as well as vascular compliance.9 In animals, high-fat feeding attenuated cardiac hypertrophy and remodeling,10,11 whereas high-carbohydrate feeding accelerated the process.12 Excessive simple sugars and saturated fatty acid ingestion worsened cardiac structure and function.13,14 In contrast, n-3 polyunsaturated fatty acid supplementation attenuated cardiac hypertrophy and fibrosis in rats.15,16 Therefore, in addition to caloric intake, macronutrient content and composition could affect LV mass and ventricular function during energy restricted diets. Carbohydrate-restricted and fat-restricted diets are commonly prescribed.17 Whether macronutrient content, without changing physical activity, affects hypocaloric diet-induced changes in LV mass and function has not been investigated in humans. The issue is important given the independent prognostic role of LV mass on cardiovascular events.3,4,18 We quantified LV mass by cardiovascular MRI, a highly sensitive and reproducible method to detect LV mass and volume changes.19 We hypothesized that a reduced-carbohydrate diet with a concomitant relative increase in dietary fat may be more effective in decreasing LV mass in...

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overweight and obese subjects compared to a fat-reduced diet. Furthermore, we tested for influences of diet-associated changes in blood pressure, glucose homeostasis, and fatty acid composition on changes in LV mass.

**Patients and Methods**

**Patients**
We included overweight and obese subjects using no medications. The study was performed in accordance with the Declaration of Helsinki, current institutional guidelines, and good clinical practice. Our Institutional Review Board approved the study and written informed consent was obtained before entry. Methodological details are provided in the online Data Supplement (http://hyper.ahajournals.org).

**Study Design**
The analysis is part of a prospective randomized study conducted in an academic clinical research center between March 2007 and June 2010. The B-SMART study (ClinicalTrials.gov Identifier: NCT00956566) compared weight loss and associated metabolic and cardiovascular markers with reduced-carbohydrate and reduced-fat hypocaloric diets. All subjects were submitted to anthropometric, metabolic, and exercise testing and cardiac MRI before and after 6 months on a hypocaloric diet with either reduced carbohydrate or reduced fat content. In both groups, we reduced energy content of the baseline food protocol by 30% to a minimum of 1200 kcal/d.

**Assessment**
After an overnight fast, we determined body weight, waist circumference, and height in a standardized fashion. We assessed lean body mass and fat mass by bioimpedance analysis (BIA 5 series; Denner, Feldmeilen, Switzerland). After a resting period of at least 5 minutes, office blood pressure was determined as a mean of 3 consecutive records using an appropriately sized cuff (Critikon; Dynamap, Tampa, FL). After another overnight fast, subjects underwent cardiac MRI studies and physical fitness testing on a bicycle ergometer. After an additional overnight fast, subjects underwent cardiac MRI studies and physical fitness testing on a bicycle ergometer. In addition, subjects underwent 24-hour blood pressure monitoring every 20 minutes between 6:00 AM and 10:00 PM and every 30 minutes during the night (SPACELABS 90207; Spacelabs Healthcare, Feucht, Germany). We determined glucose, insulin, and lipoproteins by standard methods in a certified laboratory and calculated the homeostasis model assessment index. We measured high-sensitivity C-reactive protein, high-molecular-weight adiponectin, relative n-3 polyunsaturated fatty acids intake. Fat and carbohydrate composition is shown in Table S2 (online Data Supplement, http://hyper.ahajournals.org), energy intake was similarly reduced with both dietary interventions. Table S1 also illustrates changes in fat and carbohydrate ingestion for both groups during diet. In the reduced fat group, fat ingestion was decreased, whereas carbohydrate and protein ingestion remained largely unchanged. In the reduced-carbohydrate group, we observed a moderate increase in protein and decrease in fat intake in addition to the significant decrease in carbohydrate intake. Fat and carbohydrate composition is shown in Table S2 (online Data Supplement, http://hyper.ahajournals.org).

**Sample Size and Statistical Analysis**
The B-SMART study had the primary goal to compare weight loss and metabolic, and exercise testing and cardiac MRI before and after 6 months. Both groups showed similar changes in LV mass and metabolic parameters (Table 2). Total body fat, relative n-3 and reduced-carbohydrate diet (data not shown). Cardiac output similarly decreased with reduced-carbohydrate diet and reduced-fat diets (Table 2). Seven percent (3 of 41 subjects) in the reduced-carbohydrate and 12% (6 of 49 subjects) not significant between interventions). End-diastolic and end-systolic volumes, stroke volume, ejection fraction, and ratio of early peak filling rate to atrial peak filling rate did not change with either diet. Cardiac output similarly decreased with reduced-carbohydrate diet and reduced-fat diets (Table 2). Seven percent (3 of 41 subjects) in the reduced-carbohydrate and 12% (6 of 49 subjects) not significant, (χ²) test in the reduced-fat group had high blood pressure at baseline (>140 mm Hg systolic and/or >90 mm Hg diastolic). Office blood pressure and 24-hour systolic blood pressure decreased in both groups, whereas 24-hour diastolic blood pressure did not change (Figure 2).

In univariate correlation including all subjects, absolute LV mass changes with intervention were associated with changes in body weight (r=-0.35; P<0.01), body mass index (r=-0.30; P<0.01), total body fat (r=0.44; P<0.001), relative n-3 polyunsaturated fatty acids intake (r=-0.29; P<0.01), and high-molecular-weight adiponectin (r=-0.33; P<0.01). In contrast, changes in office and 24-hour systolic and diastolic blood pressures and leptin were not correlated to LV mass changes. We conducted a multivariate regression analysis with diet, gender, changes in body weight, total body fat, cardiac output, homeostasis model assessment index, high-molecular-weight adiponectin, relative n-3 polyunsaturated fatty acids intake, and high-density lipoprotein cholesterol.
fatty acids intake, and 24-hour blood pressure as independent variables. In a stepwise backward regression analyses, only changes in body weight and changes in relative n-3 polyunsaturated fatty acids intake, respectively (β=0.33; P=0.02; β=−0.27; P=0.03), significantly predicted LV mass changes with diet. The model explained 45% of the total variation in LV mass changes with diet.

**Discussion**

The main finding of our study is that reduced-fat and reduced-carbohydrate hypocaloric diets similarly reduce LV mass in overweight and obese subjects. Apparently, energy reduction rather than relative fat or carbohydrate content promotes LV mass regression. However, relative n-3 polyunsaturated fatty acids content weight-independently predicted left ventricular mass reduction.

Energy-restricted diets effectively reduce body weight.\(^{17}\) Furthermore, diet-induced and bariatric surgery-induced weight loss have beneficial influences on cardiac structure and function.\(^{5–7}\) Some trials observed more weight loss on reduced-carbohydrate compared with reduced-fat diets,\(^{22}\) whereas others did not.\(^{23}\) We observed similar weight loss with reduced-carbohydrate and reduced-fat diets. Both groups adhered to their assigned interventions in terms of macronutrient content. Dieticians reminded participants to keep physical activity constant throughout the study. Moreover, cardio-
reduced fat

diet interactions.

samples, 2-way ANOVA detected no significant time

10.9 52.8

11.1 51.2

9.8†

9.9† 55.9

Variable Baseline 6 mo Baseline 6 mo

EDV, mL 157±27 154±27 161±32 159±29

EDV index, mL/m² 76.4±10.5 78.5±10.5 78.4±9.6 80.1±9.2

ESV, mL 62±15 62±15 64±17 64±16

ESV index, mL/m² 30.3±6.6 31.7±7.6 30.9±6.0 32.1±5.6

Heart rate, bpm 70±10 67±6† 66±8 63±6†

Stroke volume, mL 97±22 92±17 98±19 95±17

Stroke volume, mL/m² 47.2±9.1 46.7±6.0 49±19 96±17

Cardiac output, L/min 6.7±1.3 6.1±0.9† 6.5±1.1 5.9±1.1†

Cardiac output, L/min/m² 3.3±0.6 3.1±0.4* 3.2±0.6 3.0±0.5*

Ejection fraction, % 61±6 60±6 61±5 60±5

PFRₒ/PFRₚ ratio 1.45±0.60 1.39±0.58 1.47±0.45 1.36±0.52

EDV indicates end-diastolic volume; ESV, end-systolic volume; LV, left ventricular.

PFRₒ/PFRₚ: early peak filling rate/atrial peak filling rate. m²: indexed to body surface (Mosteller formula). No significant differences were detected between parameters at baseline as analyzed by Student t test for unpaired samples.

Data are mean±SD.

*P<0.05, **P<0.01 vs baseline as assessed by Student t test for paired samples, 2-way ANOVA detected no significant time<diet interactions.

In rodents, the fat-to-carbohydrate ratio in chow influenced cardiac structure and function.10,11 Similarly to our study, a previous publication reported similar LV mass changes in patients assigned to reduced-carbohydrate and reduced-fat diets. LV mass reduction at 6-month follow-up was paralleled by improved longitudinal diastolic but unchanged in systolic function. However, results were not separately reported for both intervention groups.7 Both studies cannot be directly compared because participants in this study were more obese, more insulin-resistant, and had a more diverse ethnic background. Moreover, participants were advised to increase physical activity, which is known to influence cardiac function.24 Another study recently described negative effects of an 8-week very-low-carbohydrate diet on systemic arterial stiffness.9 However, our study suggests that modest changes in dietary carbohydrate in the setting of a hypocaloric diet do not translate into a differential blood pressure and LV response. We suggest that the limited impact of macronutrient composition on LV mass in patients may be explained by the modest carbohydrate or fat restriction compared to dietary manipulations in rodents.12,13,16 Species differences in the susceptibility to dietary interventions also may be involved.

Micronutrients appear to affect cardiac remodeling and function. The n-3 polyunsaturated fatty acid supplementation attenuated cardiac hypertrophy and fibrosis and prevented upregulation of genes associated with heart failure in rats.15,16 In our subjects eating a reduced-carbohydrate diet, sucrose ingestion decreased whereas polyunsaturated fatty acid ingestion increased relative to total energy intake. However, these positive changes in dietary composition may have been counterbalanced by increased saturated fatty acid ingestion. Excessive saturated fatty acid ingestion coupled with impaired mitochondrial fatty acid oxidation could facilitate ceramide generation, thus promoting cardiomyocyte apoptosis and dysfunction.25,26 We observed that changes in relative

Figure 2. Response of systolic and diastolic office blood pressure (BP) (upper panels) and 24-hour systolic and diastolic blood pressure (lower panels) after 6 months of reduced carbohydrate (CHO) or reduced fat diet. Data are mean±SEM. *P<0.05, **P<0.01 vs baseline.
n-3 polyunsaturated fatty acid ingestion predicted changes in LV mass. The observation might suggest a role of n-3 polyunsaturated fatty acids in cardiac remodeling. Because we did not analyze individual n-3 free-fatty acids (eg, 20:5 n-3 or 22:6 n-3), we cannot rule out the possibility that various n-3 fatty acids have a differential impact on LV mass during a dietary intervention. Epidemiological and clinical trials reported a reduced incidence of cardiovascular disease and mortality with n-3 fatty acids.27 Particularly n-3 fatty acids found in fish oil, namely eicosapentaenoic (20:5 n-3) and docosahexaenoic acid (22:6 n-3), may lower heart failure incidence and cardiovascular events.28

To what extent an increase in LV mass directly results from obesity or from associated conditions, such as hypertension, impaired glucose homeostasis, fat distribution, or physical fitness, is unclear.29–32 Several studies showed additive effects of increased blood pressure and body mass index on LV mass.30,33 Overt diabetes mellitus, insulin resistance, and body fat redistribution may further exacerbate LV hypertrophy.32,34–36 In our study, LV mass reduction was related to overall body weight reduction in univariate and multivariate analysis, but not to changes in 24-hour blood pressure or measurements of insulin resistance. This finding may be explained by the nearly normal blood pressure and insulin sensitivity in our subjects. Diet-induced weight loss appears to be a particularly strong trigger for LV mass regression compared with changes in blood pressure or glucose homeostasis. Blood pressure reduction likely contributes to LV mass regression with weight loss through improved cardiac loading conditions, albeit to a lesser and time-dependent degree.37 A multivariate analysis including important cardiovascular and metabolic variables explained only 45% of LV mass changes with weight loss. Thus, in addition to body weight loss and fatty acid composition, other unknown mechanisms contribute to LV mass regression with weight loss. Blunted renin-angiotensin system activity and sympathetic activation could contribute to the LV mass reduction by weight loss.38–40 These mechanisms are also involved in altered hemodynamics after dietary weight loss, which is reflected by reduced cardiac output and heart rate in our study.

The main limitation of our study is that a 6-month weight loss period may not be sufficiently long to observe influences of macronutrient content on LV mass. An influence of macronutrient composition could be unmasked during weight stabilization or regain. Because of the small number in our study, the results for men should be interpreted with caution. The use of MRI instead of echocardiography may have influenced the assessment of changes in diastolic function during diet. However cardiac MRI-derived ratio of early peak filling rate to atrial peak filling rate has been recently shown to reflect respective echocardiography parameters.41 Furthermore, our study does not exclude that more extreme changes in dietary fat and/or carbohydrate affect LV mass in a weight-independent fashion. However, we suggest that the changes in macronutrient content in our study reflect typical western dietary patterns. Finally, although the prespecified goal of our study was to assess influences of macronutrients and micronutrients on cardiovascular and metabolic risk markers, dietary n-3 polyunsaturated fatty acids was not a prespecified end point and has to be interpreted with caution.

We conclude that over a 6-month period, caloric restriction results in reductions of LV mass irrespective of the relative fat or carbohydrate content during diet in nondiabetic overweight and obese subjects. This response seems to be more associated with changes in adiposity than hemodynamic or metabolic factors per se. Our study also suggests that an increased proportion of n-3 polyunsaturated fatty acids may contribute to LV mass reduction in a body weight-independent manner.

Perspectives
Obesity-related increases in LV mass contribute to heart failure and mortality. Caloric restriction is able to reduce LV mass in conjunction with weight loss. However, it is not clear whether alterations in macronutrient content during diet play a role in modulating this response. Experiments in rodents suggested an influence of the relative contribution of carbohydrates and fat to total energy intake on cardiac morphology and function. In addition, the proportion of simple sugar and unsaturated and polyunsaturated fatty acids are reported to play a role in this regard. We found that reductions in total energy intake irrespective of the relative contribution of fat and carbohydrate content to total caloric intake reduce LV mass in overweight and obese subjects. Interestingly, the proportion of n-3 polyunsaturated fatty acids was a factor predicting LV mass reduction in a body weight-independent manner. Given the importance of increasing LV mass in the pathogenesis of heart failure, the value of dietary modulations in humans deserve to be studied in more detail.

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Disclosures
None.

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Online supplement

LEFT VENTRICULAR MASS AND FUNCTION WITH REDUCED-FAT AND REDUCED-CARBOHYDRATE HYPOCALORIC DIETS IN OVERWEIGHT AND OBESE SUBJECTS

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*SH and WU contributed equally to the manuscript
Methods

Patients. All subjects completed a comprehensive medical evaluation including a dietary and physical activity record for seven consecutive days before study participation. Subjects reporting more than 2 hours of physical activity per week were excluded. We also excluded subjects with type 2 diabetes, acute or chronic infections, any disease requiring treatment, and pregnant or nursing women. Subjects were advised to continue their current physical activity level throughout the study.

Study design. Study nurses and physicians screening and enrolling volunteers were blinded for the treatment assignment, whereas dietitians were not. For subject allocation, we utilized a computer-generated random numbers list. The randomization sequence was created using SPSS 18 (SPSS, Inc., Chicago, IL, USA) statistical software and subjects were assigned to reduced carbohydrate or reduced fat diet with a 1:1 allocation using random block sizes of 2, 4, and 6. After randomization, subjects provided a baseline 7-day dietary record which was analyzed for macronutrient content including fatty acids and carbohydrate composition using professional nutrition analysis software (Optidiet V3.1.0.004, GOE, Linden/Germany) that is based on nutritional content of food as provided by the German National Food Key.

Dietary specifications. Nutrition counselling aimed at achieving a daily macronutrient intake ≤90 g carbohydrates, 0.8 g protein per kg body weight, and a minimum of 30% fat in the reduced carbohydrate group, and a fat intake of ≤20% of total energy intake, 0.8 g protein per kg body weight, and the remaining energy content provided by carbohydrates in the reduced fat group. All participants attended either reduced carbohydrate or reduced fat weekly group sessions run by nutritionists throughout the 6-months weight reduction program, providing background information on healthy food choices for each group. In addition, individual counselling by a nutritionist including analysis of a 7-day food protocol took place every 2 months during the 6 months intervention, to address individual questions, and to monitor adherence to the diet.

Cardiac MRI. We applied a 1.5 Tesla MR scanner (Sonata and Avanto, Siemens Medical Solutions AG, Erlangen, Germany) to determine cardiac morphology and function. After initial anatomic scout images had been obtained, we performed high temporal resolution cine imaging with a balanced steady-state free precession (b-SSFP) sequence (TR 16.3 ms, TE 1.15ms, 64 phases, matrix 208 x 256, FOV 325 x 400 mm², in plane resolution 1.6 x 1.6 mm², retrospective ECG-gating). We acquired a stack of contiguous short axis slices (slice thickness 7 mm, interslice gap 3 mm) during repetitive breath-holds in end-expiration. We quantified left ventricular structure and ejection fraction by manually drawing endocardial and epicardial contours in end-diastole and end-systole using dedicated software (MASS7.1, Medis AG, Leiden, Netherlands). Left ventricular mass was indexed for height (g/m) and height (g/m².7). For assessment of left ventricular diastolic function, we acquired high-temporal resolution cine images in horizontal and vertical long axes. We followed endocardial contours in all diastolic phases and calculated left ventricular volumes using a biplane model. Peak filling rates in the early (PFR_E) and in the atrial (PFR_A) filling phase were derived from resulting left ventricular volume-time curves using Origin 8.0 (OriginLab Corporation, Northampton, USA).

Exercise test. Exercise started at a workload of 25 watts and increased every 2 min by 25 Watt until the subjects could not maintain the requested 60 rpm pedal frequency. We monitored gas exchange and power output continuously using an open spirometric system (Vmax Spectra Model 229D analyzer, SensorMedics, Yorba...
Linda, USA). Oxygen uptake and carbon dioxide production was recorded breath-by-breath and averaged in 10 sec intervals.

**Biochemical measurements and calculations.** HOMA-IR was calculated from fasting insulin and glucose by (insulin [µU/ml] x glucose [mmol/l]) / 22.5.3 We measured high sensitive-CRP and high molecular weight adiponectin [both in µg/ml] by sandwich ELISA: hs-CRP (BioVendor, Heidelberg, Germany, #RH961CRP01HR), intraassay coefficient of variation (CV) 3.8% and interassay CV 5.2%. High-molecular weight adiponectin (ALPCO Immunoassays, Salem, NH, USA, #47-ADPHU-E01), intraassay CV 6.2% and interassay CV 5.3%. Leptin (BioVendor, Heidelberg, Germany, #RD191001100), intraassay CV 4.2% and interassay CV 6.7%.

**References**

Table S1. Energy and macronutrient intake, and body weight

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<tr>
<th>visits (month)</th>
<th>baseline</th>
<th>month 2</th>
<th>month 4</th>
<th>month 6</th>
<th>diet x time (interaction)</th>
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<td>2072 ± 543</td>
<td>1621 ± 450*</td>
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<td>1682 ± 336*</td>
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<tr>
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<td>109 ± 46*</td>
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<td>86.5 ± 16.8*</td>
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*p<0.01 vs. baseline, tested by ANOVA for repeated measures with Bonferroni´s post hoc tests, time x diet interactions were analyzed by two-way ANOVA for repeated measures. Data are mean ± SD.

Table S2. Dietary composition

<table>
<thead>
<tr>
<th>micronutrients</th>
<th>baseline</th>
<th>after diet</th>
<th>baseline</th>
<th>after diet</th>
<th>diet x time (interaction)</th>
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<td>saturated FA, %</td>
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<td>15.4 ± 3.4*</td>
<td>14.3 ± 2.4</td>
<td>10.0 ± 2.8†</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>n-3 PUFA, %</td>
<td>0.75 ± 0.39</td>
<td>1.14 ± 1.60†</td>
<td>0.70 ± 0.21</td>
<td>0.74 ± 0.25</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>n-6 PUFA, %</td>
<td>3.79 ± 1.13</td>
<td>5.82 ± 2.79†</td>
<td>3.95 ± 1.20</td>
<td>3.91 ± 2.22</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>sucrose, %</td>
<td>11.5 ± 4.1</td>
<td>4.8 ± 2.6†</td>
<td>11.8 ± 5.5</td>
<td>10.6 ± 3.7</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>

Data are given as percentage of total energy intake, FA: fatty acids, PUFA: polyunsaturated fatty acids, no significant differences were detected between parameters at baseline as analyzed by Student’s t-test for unpaired samples,*=p<0.05, †=p<0.01 vs. baseline, as assessed by Student´s t-test for paired samples. Time x diet interactions were analyzed by two-way ANOVA for repeated measures, Data are mean ± SD.
Figure S1. Patient disposition during the course of study