

**Citation:**

Keogh JB, Brinkworth GD, Noakes M, Belobrajdic DP, Buckley JD, Clifton PM. Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. *Am J Clin Nutr.* 2008 Mar;87(3):567-76.

**PubMed ID:** [18326593](#)

**Study Design:**

Randomized Controlled Trial

**Class:**

A - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

The aim of the study was to examine the effect of a very-low-carbohydrate, high-saturated-fat weight-loss diet compared with that of an isocaloric conventional high-carbohydrate, low saturated-fat diet on flow mediated dilatation, concentrations of endothelial derived factors, adiponectin, and cardiometabolic risk factors after weight loss.

**Inclusion Criteria:**

Overweight and obese men and women with abdominal obesity and at least one other additional risk factor for the metabolic syndrome according to the criteria of the International Diabetes Federation.

**Exclusion Criteria:**

- History of liver, cardiovascular, peripheral vascular, respiratory, or gastrointestinal disease
- Diabetes
- Malignancy

**Description of Study Protocol:**

**Recruitment** by public advertisement

**Design:** Randomized, controlled parallel trial

**Blinding used:** participants blinded

**Intervention (if applicable)**

Participants were matched for age, sex, and BMI and were randomly assigned to either an energy restricted very-low-carbohydrate, high-saturated-fat diet (LC) or an isocaloric conventional high-carbohydrate, low-saturated-fat diet (HC) for 8 weeks. Measurements were taken at baseline (week 0) and after weight loss (week 8). Every two weeks during the intervention, participants came to clinic for a weight check and a consultation with a dietitian. Apart from the dietary intervention, subjects were asked to maintain their usual lifestyle throughout the study.

- LC diet: 35% of energy as protein, 61% as fat, 20% as saturated fat, and 4% as carbohydrate
- HC diet: 24% energy as protein, 30% as fat, carbohydrate
- Diets were designed to provide moderate energy restriction of 30% for 8 wk.
- Key foods for each diet were supplied every 2 weeks for the 8 weeks to aid compliance.
- Diet plan was structured to include specific daily quantities of foods to ensure the correct macronutrient and energy requirements. These foods were listed in a food record that the participants completed daily.
- Detailed dietary advice, meal planning, and recipe information were provided at baseline and every 2 weeks by a qualified dietitian. Scales for weighing food were provided. Three consecutive days (1 weekend and 2 weekdays) from the semiquantitative food record of each 2-wk period were analyzed (12 days in total), while the volunteer was present to ensure accuracy, with a computerized database of Australian foods (FOODWORKS Professional Edition, version 4).

### Statistical Analysis -

- Data were tested for normality, and all variables were normally distributed.
- One factor analysis of variance was used to compare baseline characteristics and dietary data.
- The effect of the intervention was assessed by using repeated-measures analysis of variance, with time as the within-subject factor and diet (LC compared with HC) and sex as the between-subjects factors and change in weight as a covariate where appropriate.
- Correlational and regression analysis was used to determine relations of changes between variables.
- Univariate analysis of covariance was used to determine differences between diets after weight loss, with baseline values as a covariate.
- Statistical significance was set at 0.05.

### Data Collection Summary:

#### Timing of Measurements

Baseline (week 0) and after weight loss (week 8) - attended clinical research unit after an overnight fast on 2 consecutive days.

- Day 1 - Height, weight, blood pressure
- Day 1 - Venous blood sample to measure lipids, glucose, insulin, folate, homocysteine, and C-reactive protein (CRP)
- Day 2 - Venous blood sample to measure lipids, plasma ketone bodies, and the augmentation index (AI).
- Day 2 - subsample of subjects had an additional blood sample to measure adhesion molecules, plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator (tPA), and adiponectin.
- 24-hour urine sample

Throughout the intervention, participants attended the clinic fortnightly for a weight check.

#### Dependent Variables

- Height - measured to nearest 0.1cm with stadiometer; barefoot
- Weight - measured to nearest 0.05kg with calibrated electrical digital scales; wearing light clothing and no footwear
- Body composition - measured using DXA
- Abdominal fat content - estimated from regional analysis of the DXA scan by drawing a quadrilateral box with the base of the box touching the top of the iliac crest, the lateral

borders extending to the edge of the abdominal soft tissue, and upper right margin touching the most inferior aspect of the ribs.

- Endothelium dependent flow-mediated dilation (FMD) of the right brachial artery
- Aortic pulse wave velocity (PWV) - measured via Doppler recordings in the carotid and femoral arteries
- AI
- Resting blood pressure (mean of 3 measurements)
- Lipids (fasting blood sample)
- Apolipoprotein B (apo B) (fasting blood sample)
- Insulin (fasting blood sample)
- CRP (fasting blood sample)
- Homocysteine (fasting blood sample)
- Folate (fasting blood sample)
- Adiponectin (fasting blood sample)
- Adhesion molecule measurements (fasting blood sample) - E selectin, P selectin, I-CAM
- Blood glucose (fasting blood sample)
- Urea/creatinine ratio - used to assess dietary compliance

### **Independent Variables**

- Randomly assigned to either an energy restricted very-low-carbohydrate, high-saturated-fat diet (LC) or an isocaloric conventional high-carbohydrate, low-saturated-fat diet (HC) for 8 weeks.

### **Control Variables**

## **Description of Actual Data Sample:**

### **Initial N:**

- 1150 responded to advertisement
- 349 returned questionnaires (of those that returned questionnaires, 145 were ineligible)
- 204 subjects screened
- 121 were eligible for participation
- 117 were randomized (4 withdrew prior to randomization; 11 withdrew before the intervention started; 3 withdrew due to work or personal reasons)
  - LC group: n=57
  - HC group: n=50

### **Attrition (final N):**

- LC group: personal reasons: n=1; illness unrelated to study: n=1; unable to comply with diet: n=1; changed to HC diet: n=2
- HC group: 1 lost to follow-up; 1 unable to comply with diet
- Completers: 52 in LC group; 47 in HC group

**Age:** 24-64 years old

**Ethnicity:** Not mentioned

### **Other relevant demographics:**

- 34 were taking antihypertensive medication (8 excluded from the blood pressure analysis)

- 23 taking lipid-lowering medication (3 excluded from the lipid analysis)

**Anthropometrics** Participants in the LC and HC groups were the same at baseline for age, body mass index (BMI), systolic blood pressure, glucose, insulin, total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol. The HC group had a higher diastolic blood pressure ( $78 \pm 12$  mmHg) compared to the LC group ( $73 \pm 12$  mmHg).

**Location:** Adelaide, Australia

## Summary of Results:

### Key Findings

- Mean FMD did not change significantly ( $p=0.55$ ) with either diet.
- PWV improved with both diets ( $p<.01$ )
- Endothelial markers, E- and P-selectin, intracellular, and cellular-adhesion molecule-1, tissue type plasminogen activator, and plasminogen activator inhibitor-1 decreased ( $p<.001$ ), with no diet effect.
- Adiponectin did not change significantly.
- More weight ( $p<.05$  for diet x time interaction) and more abdominal fat mass ( $p<.05$  for diet x time interaction) were lost with the LC than with the HC.
- LDL cholesterol decreased more with the HC than with the LC ( $p<.05$ , time x diet), and CRP decreased more with the HC than with the LC ( $p<.05$  for diet x time).
- Folate decreased with the LC and increased with the HC ( $p<.05$ , time;  $p<.001$  for diet x time interaction).

Variables	Treatment Group Mean, CI.	Control group Mean, CI.	Statistical Significance of Group Difference
Energy (kJ)	6608 $\pm$ 664	6590 $\pm$ 717	NS
Protein (g) % energy	(133 $\pm$ 10) 35.0 $\pm$ 2.0	(87 $\pm$ 9) 24.1 $\pm$ 1.6	<.001
Fat (g) % energy	(103 $\pm$ 13) 58.5 $\pm$ 2.6	(47 $\pm$ 7) 27.8 $\pm$ 3.4	<.001
Carbohydrate (g) % energy	(20 $\pm$ 4) 5.1 $\pm$ 0.9	(172 $\pm$ 26) 46.7 $\pm$ 3.4	<.001
Alcohol (g) % energy	(3 $\pm$ 4) 1.4 $\pm$ 1.8	(3 $\pm$ 4) 1.5 $\pm$ 1.6	NS
Saturated fat (g) % energy	(37 $\pm$ 5) 21 $\pm$ 2	(10 $\pm$ 2) 6 $\pm$ 1	<.001
PUFA (g) % energy	(14 $\pm$ 3) 8 $\pm$ 1	(12 $\pm$ 2) 7 $\pm$ 1	<.001
MUFA (g) % energy	(45 $\pm$ 6) 25 $\pm$ 2	(21 $\pm$ 4) 12 $\pm$ 2	<.001
Cholesterol (mg)	596 $\pm$ 89	140 $\pm$ 28	<.001
Fiber (g)	13 $\pm$ 2	32 $\pm$ 5	<.001
Vitamin C (mg)	140 $\pm$ 41	178 $\pm$ 61	<.001
Folate (microgram)	318 $\pm$ 47	348 $\pm$ 60	<.01
Calcium (mg)	908 $\pm$ 129	813 $\pm$ 84	<.001

n-	0.53	0.13±	.05
3 VLC fatty acids	±0.39	0.07	
n-	10.61	8.08	.06
6 Linoleic acid	±1.84	±1.35	
n-	0.52	0.37	.05
3 -Linolenic acid	±0.06	±0.09	
Weight change (kg)	-7.5±2.6	-6.2±2.9	<.01 (diet x time)
Fat mass (kg)	-5.3±2.5	-4.9±3.6	
Fat (%)	-2.6±2.6	-2.4±2.5	
Abdominal fat (%)	-0.6±0.4	-0.4±0.3	

### Author Conclusion:

An LC does not impair FMD. We observed beneficial effects of both diets on most of the CVD risk factors measured.

### Reviewer Comments:

#### Strengths:

- *Randomized controlled trial*
- *Statistically sound - verification of assumptions*
- *Low attenuation*

#### Weaknesses:

- *Relatively short term (8 weeks)*

### Research Design and Implementation Criteria Checklist: Primary Research

#### Relevance Questions

- |    |   |     |
|----|---|-----|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?   | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?  | Yes |

4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes
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### Validity Questions

<b>1.</b>	<b>Was the research question clearly stated?</b>	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
<b>2.</b>	<b>Was the selection of study subjects/patients free from bias?</b>	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
<b>3.</b>	<b>Were study groups comparable?</b>	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
<b>4.</b>	<b>Was method of handling withdrawals described?</b>	Yes

4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
<b>5.</b>	<b>Was blinding used to prevent introduction of bias?</b>	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
<b>6.</b>	<b>Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?</b>	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	Yes
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A

<b>7.</b>	<b>Were outcomes clearly defined and the measurements valid and reliable?</b>	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
<b>8.</b>	<b>Was the statistical analysis appropriate for the study design and type of outcome indicators?</b>	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
<b>9.</b>	<b>Are conclusions supported by results with biases and limitations taken into consideration?</b>	No
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	No
<b>10.</b>	<b>Is bias due to study's funding or sponsorship unlikely?</b>	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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