Are low-fat diets good for everyone?
Effects of dietary intake on LDL subclass phenotype and risk of coronary heart disease

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Assumptions Underlying Low-Fat Dietary Recommendations

- Individuals on low-fat diets are more likely to consume less saturated fat, which in turn can lead to lower LDL cholesterol
- Fat is calorie-dense, hence lower fat diets will lead to less calorie intake and weight loss
- The population as a whole can benefit from reducing dietary fat
- Substituting carbohydrates for fats is healthier

There are a range of lipid and lipoprotein responses to low-fat diets

Genetics of Lipoproteins and Diet (GOLD)
688 men and women; 20-24% vs. 40-46% fat, 4-6 weeks,

LDL Consists of Multiple Discrete Subclasses

Large
Medium
Small
- Reduced uptake from blood
- Greater binding in artery wall
- Greater oxidative susceptibility

Distribution of subclasses is independent of total LDL cholesterol

Levels of small LDL are independently predictive of CAD risk
Quebec Cardiovascular Study

St. Pierre et al., Circulation 104:2295, 2001
Model for Origins of LDL Subclasses and Atherogenic Dyslipidemia of Obesity

Determinants of LDL Subclass Phenotypes
- Heritability ~ 40-75%
- Modifying factors: age, gender, adiposity/insulin resistance, diet?

LDL Subclass Phenotypes in Healthy Men
Does LDL response to low-fat diet differ between phenotypes?

Changes in LDL-Cholesterol Low-Fat (20-24%) vs. High-Fat (40-46%)

Change in Apoprotein B with Low-Fat Diet
One ApoB molecule/LDL particle; ApoB is an index of number of particles

Changes in LDL Subclasses with Low-Fat High-Carbohydrate Diet

Adapted from Berneis and Krauss, J Lipid Res 43:1155, 2002
Dreon et al. FASEB Journal, 8:121, 1994
Differing Mechanisms for Reduction in LDL Cholesterol in LDL Pattern A and B

Pattern A
- Larger LDL
- Less cholesterol per particle
- Similar number of particles

Pattern B
- Smaller LDL
- Reduced number of particles

Cholesterol
ApoB

Low-fat, high carbohydrate diet can induce expression of phenotype B

Prevalence of LDL Subclass Phenotype B is Related to Percent Dietary Carbohydrate

Data from 6 studies in healthy men (n = 768)

% Dietary Carbohydrate

% Phenotype B

r = 0.93
P <0.0001

Summary (1)

- Individuals with LDL phenotype B, a high-risk heritable trait characterized by a predominance of small dense LDL, show greatest LDL reduction on diets low in total and saturated fat - this subgroup may account for much of the LDL reduction attributable to such diets.
- The LDL reduction with low fat in phenotype B subjects is restricted to less atherogenic medium and larger LDL.
- A high proportion of healthy individuals are predisposed to induction of phenotype B with high carbohydrate-low fat diets.

Study Design

Subjects: 178 healthy men with BMI 26-35 (mean 29)

Baseline diet 1 wk

Randomization

Basal Control

Lower Carbohydrate

Higher Carbohydrate

Pre w/loss 3 wk

Baseline diet 1 wk

Randomization

Basal Control

Lower Carbohydrate

Higher Carbohydrate

Post w/Loss 4 wk

Weight loss 1 kg/wk, 5 wk

Baseline diet 1 wk

Randomization

Basal Control

Lower Carbohydrate

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Lower Carbohydrate

Higher Carbohydrate

Post w/Loss 4 wk

Weight loss 1 kg/wk, 5 wk
Low Carbohydrate Diets Reverse Phenotype B

129 overweight/obese men randomized to 39% and 26% carbohydrate diets.

Baseline diet vs. Low carbohydrate diets

LDL pattern: B (•) A (▲)

Prevalence of LDL Phenotype B as a Function of Dietary Carbohydrate Before and After Weight Loss

Krauss et al., 2004

Atherogenic lipoprotein phenotype B can be reversed by either reduced dietary carbohydrate or weight loss.

Changes in LDL Cholesterol from Baseline

How do these effects compare with those predicted on higher carbohydrate diets?

Apparent Benefits of Reduced Dietary Carbohydrate and/or Increased Protein on LDL-C Response to Dietary Fat

Changes in LDL-C (mg/dL) Predicted* Observed

Higher saturated fat +9 +1
Lower saturated fat -1 -11

* Mensink et al. AJCN 77:1146, 2003

Small LDL levels are reduced by lower carbohydrate intake independent of saturated fat.
Higher saturated fat intake raises levels of large LDL

Changes in Total/HDL Cholesterol with Carbohydrate Reduction and Weight Loss

Summary (2) Effects of Reduced Carbohydrate and Weight Loss on LDL Particles

Changes in LDL Cholesterol from Baseline

Do changes differ in phenotype B vs. A?
**Implications of Findings for Dietary Recommendations**

- Moderate weight loss can substantially improve the atherogenic dyslipidemia of obesity and metabolic syndrome.
- Lower carbohydrate intake can achieve similar benefits and is particularly advisable if adequate weight loss is not achieved.
- Limitation of saturated fat intake is not required to improve atherogenic lipid indices in the setting of a lower carbohydrate diet (but some individuals are genetically predisposed to adverse effects of saturated fat).

**Changes in Small LDL with Reduced Dietary Carbohydrate Are Correlated with Changes in Triglyceride**

![Graph showing correlation between changes in Small LDL mass and dietary carbohydrate intake](image)

$r=0.5, p<0.0001$

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